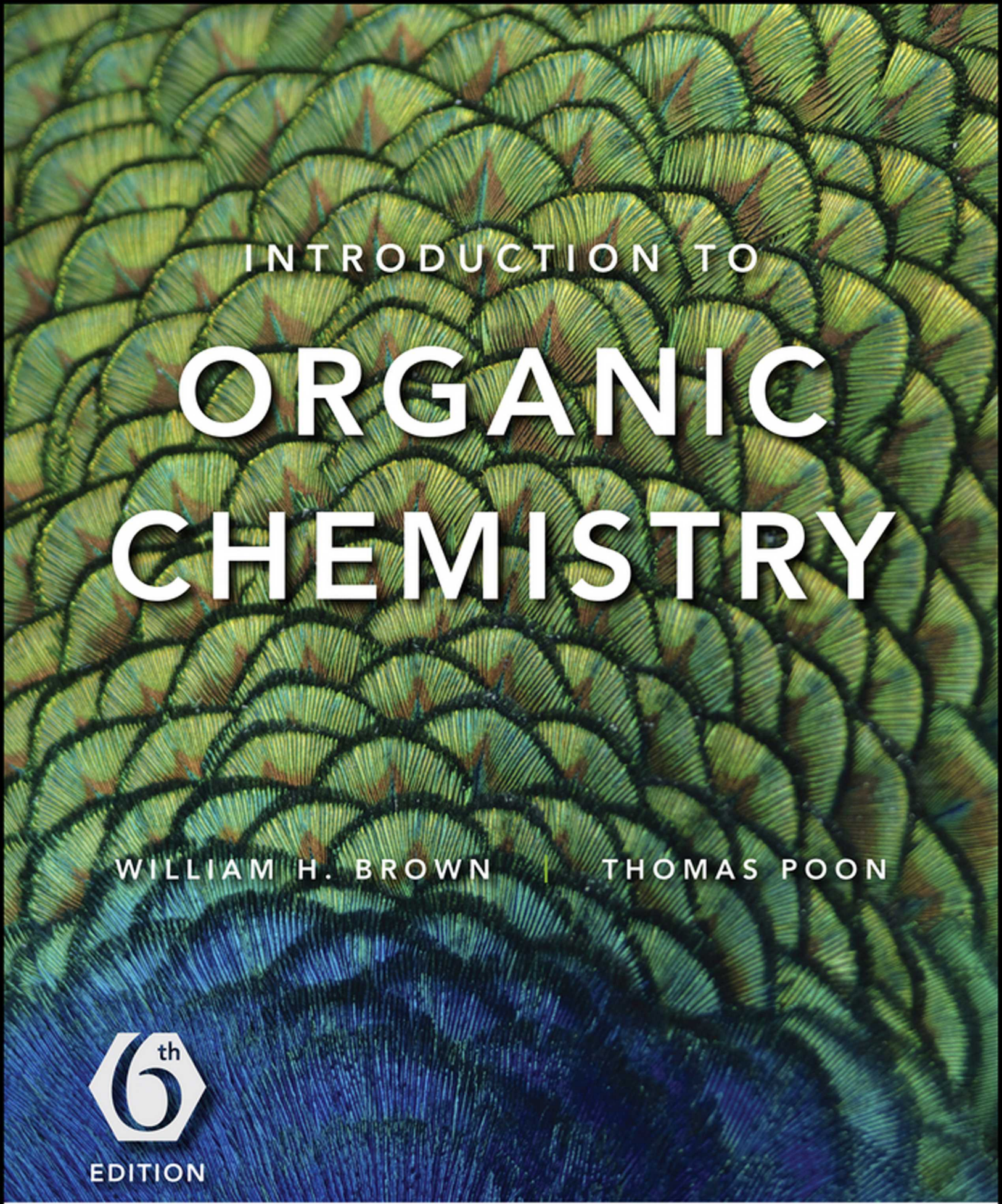

Wiley Binder Version

WILEY

Introduction to
Organic Chemistry

SIXTH EDITION

WILLIAM H. BROWN
Beloit College

THOMAS POON
Claremont McKenna College
Scripps College
Pitzer College

WILEY

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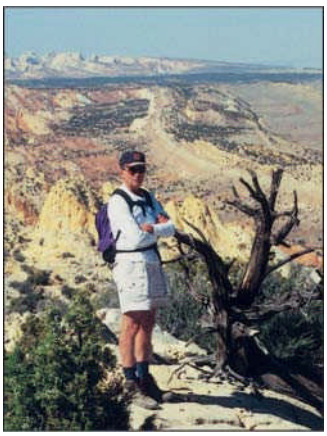
To Carolyn,
with whom life is a joy

Bill Brown

To Cathy and Sophia,
for a lifetime of adventures

Thomas Poon

ABOUT THE AUTHORS



WILLIAM H. BROWN is Professor Emeritus at Beloit College, where he was twice named Teacher of the Year. He is also the author of two other college textbooks: *Organic Chemistry* 5/e, coauthored with Chris Foote, Brent Iverson, and Eric Anslyn, published in 2009, and *General, Organic, and Biochemistry* 9/e, coauthored with Fred Bettelheim, Mary Campbell, and Shawn Farrell, published in 2010. He received his Ph.D. from Columbia University under the direction of Gilbert Stork and did postdoctoral work at California Institute of Technology and the University of Arizona. Twice he was Director of a Beloit College World Affairs Center seminar at the University of Glasgow, Scotland. In 1999, he retired from Beloit College to devote more time to writing and development of educational materials. Although officially retired, he continues to teach Special Topics in Organic Synthesis on a yearly basis.

Bill and his wife Carolyn enjoy hiking in the canyon country of the Southwest. In addition, they both enjoy quilting and quilts.

THOMAS POON is Professor of Chemistry in the W.M. Keck Science Department of Claremont McKenna, Pitzer, and Scripps Colleges, three of the five undergraduate institutions that make up the Claremont Colleges in Claremont, California. He received his B.S. degree from Fairfield University (CT) and his Ph.D. from the University of California, Los Angeles under the direction of Christopher S. Foote. Poon was a Camille and Henry Dreyfus Postdoctoral Fellow under Bradford P. Mundy at Colby College (ME) before joining the faculty at Randolph-Macon College (VA) where he received the Thomas Branch Award for Excellence in Teaching in 1999. He was a visiting scholar at Columbia University (NY) in 2002 (and again in 2004) where he worked on projects in both research and education with his late friend and mentor, Nicholas J. Turro. He has taught organic chemistry, forensic chemistry, upper-level courses in advanced laboratory techniques, and a first-year seminar class titled *Science of Identity*. His favorite activity is working alongside undergraduates in the laboratory on research problems involving the investigation of synthetic methodology in zeolites, zeolite photochemistry, natural products isolation, and reactions of singlet oxygen.

When not in the lab, he likes to play guitar and sing chemistry songs to his students and to his daughter Sophie.

CONTENTS OVERVIEW

CONTENTS

Goals of This Text

This text is designed for an introductory course in organic chemistry and assumes, as background, a prior course of general chemistry. Both its form and content have been shaped by our experiences in the classroom and by our assessment of the present and future direction of the brief organic course.

A brief course in organic chemistry must achieve several goals. First, most students who elect this course are oriented toward careers in science, but few if any intend to become professional chemists; rather, they are preparing for careers in areas that require a grounding in the essentials of organic chemistry. Here is the place to examine the structure, properties, and reactions of rather simple molecules. Students can then build on this knowledge in later course work and professional life.

Second, an introductory course must portray something of the scope and content of organic chemistry as well as its tremendous impact on the ways we live and work. To do this, we have included specific examples of pharmaceuticals, plastics, soaps and detergents, natural and synthetic textile fibers, petroleum refining, petrochemicals, pesticides, artificial flavoring agents, chemical ecology, and so on at appropriate points in the text.

Third, a brief course must convince students that organic chemistry is more than just a catalog of names and reactions. There are certain organizing themes or principles, which not only make the discipline easier to understand, but also provide a way to analyze new chemistry. The relationship between molecular structure and chemical reactivity is one such theme. Electronic theory of organic chemistry, including Lewis structures, atomic orbitals, the hybridization of atomic orbitals, and the theory of resonance are presented in Chapter 1. Chapter 2 explores the relationship between molecular structure and one chemical property, namely, acidity and basicity. Variations in acidity and basicity among organic compounds are correlated using the concepts of electronegativity, the inductive effect, and resonance. These same concepts are used throughout the text in discussions of molecular structure and chemical reactivity. Stereochemistry is a second theme that recurs throughout the text. The concept and importance of the spatial arrangement of atoms is introduced in Chapter 3 with the concept of conformations in alkanes and cycloalkane, followed by *cis/trans* isomerism in Chapters 3 (in cycloalkanes) and 4 (in alkenes). Molecular symmetry and asymmetry, enantiomers and absolute configuration, and the significance of asymmetry in the biological world are discussed in Chapter 6. The concept of a mechanistic understanding of the reactions of organic substances is a third major theme. Reaction mechanisms are first presented in Chapter 5; they not only help to minimize memory work but also provide a satisfaction that comes from an understanding of the molecular logic that governs how and why organic reactions occur as they do. In this chapter we present a set of five fundamental patterns that are foundational to the molecular logic of organic reactions. An understanding and application of these patterns will not only help to minimize memory work but also provide a satisfaction that comes from an understanding of how and why organic reactions occur as they do.

The Audience

This book provides an introduction to organic chemistry for students who intend to pursue careers in the sciences and who require a grounding in organic chemistry. For this reason, we make a special effort throughout to show the interrelation between organic chemistry and other areas of science, particularly the biological and health sciences. While studying with this book, we hope that students will see that organic chemistry is a tool for these many disciplines, and that organic compounds, both natural and synthetic, are all around them—in pharmaceuticals, plastics, fibers, agrochemicals, surface coatings, toiletry preparations and cosmetics, food additives, adhesives, and elastomers. Furthermore, we hope that students will recognize that organic chemistry is a dynamic and ever-expanding area of science waiting openly for those who are prepared, both by training and an inquisitive nature, to ask questions and explore.

New Features

- **Modified Chapter Openers** that employ a Guided Inquiry approach to capture students' attention, getting them excited about the material they are about to read.
- **Key Concept Videos:** Created by co-author Tom Poon, these videos are centered on key topics in the text, helping students better understand important concepts.

  Video lectures are denoted by the following icon which can be found throughout the text.
- **More Practice Problems:** We have added over 130 additional practice problems, while keeping in mind the care and attention instructors put into their courses by *not* changing the basic numbering of problems from the previous addition.
- **More Real World Connections:** In order to show the connections between organic chemistry and other disciplines, we have added over 40 references, either in-text or via column elements, to real world products or applications.
- We have reduced the length of the text. Chapter 19, Lipids, along with Chapter 20 Nucleic Acids, and Chapter 21, The Organic Chemistry of Metabolism, will be available in WileyPLUS and on the text website: www.wiley.com/college/brown.

Hallmark Features

- **"Mechanism"** boxes for each mechanism in the book. These Mechanism boxes serve as road maps and present mechanisms using basic steps and recurring themes that are common to most organic reaction mechanisms. This approach allows students to see that reactions have many steps in common, making the reaction easier to understand and remember.
- **"Group Learning Activities"** appear with the end-of-chapter problems and provide students with the opportunity to learn organic chemistry collaboratively, fostering more active learning.
- **"Key Terms and Concepts"** appear within the "Summary of Key Questions."
- **"How To Boxes":** Step-by-step How To guides for approaching problems and concepts that students often find difficult.

- **Chemical Connection Boxes** include applications of organic chemistry to the world around us, particularly to the biochemical, health, and biological sciences. The topics covered in these boxes represent real-world applications of organic chemistry and highlight the relevance between organic chemistry and the students' future careers.

- **"Putting It Together" Cumulative Review Questions:** In this text, end-of-chapter problems are organized by section, allowing students to easily refer back to the appropriate section if difficulties arise. We offer a section called Putting It Together (PIT) at the end of Chapters 3, 6, 10, 14, and 17. Each PIT section is structured like an exam would be organized, with questions of varying types (multiple choice, short answer, naming, mechanism problems, predict the products, synthesis problems, etc.) and difficulty.

- **Problem-Solving Strategies:** To help students overcome the challenge of knowing where to begin, we include a strategy step for every worked example in the text. The strategy step will help students to determine the starting point for each of the example problems.

- **Quick Quizzes:** A set of true or false questions, provided at the end of every chapter, is designed to test students' understanding of the basic concepts presented in the chapter. The answers to the quizzes are provided at the bottom of the page so that students can quickly check their progress, and if necessary, return to the appropriate section in the chapter to review the material.

- **Greater Attention to Visual Learning:** Research in knowledge and cognition has shown that visualization and organization can greatly enhance learning. We added over 100 callouts (short dialog bubbles) to highlight important features of many of the illustrations throughout the text. This places most of the important information in one location. When students try to recall a concept or attempt to solve a problem, we hope that they will try to visualize the relevant illustration from the text. They may be pleasantly surprised to find that the visual cues provided by the callouts help them to remember the content as well as the context of the illustration.

Organization: An Overview

Chapters 1–10 begin a study of organic compounds by first reviewing the fundamentals of covalent bonding, the shapes of molecules, and acid-base chemistry. The structures and typical reactions of several important classes of organic compounds are then discussed: alkanes; alkenes and alkynes; haloalkanes; alcohols and ethers; benzene and its derivatives; amines, aldehydes, and ketones; and finally carboxylic acids and their derivatives.

Chapter 11 introduces IR spectroscopy, and 1H-NMR and 13C-NMR spectroscopy. Discussion of spectroscopy requires no more background than what students receive in general chemistry. The chapter is freestanding and can be taken up in any order appropriate to a particular course.

Chapters 12–16 continue the study of organic compounds, including aldehydes and ketones, carboxylic acids, and finally carboxylic acids and their derivatives. Chapter 15 concludes with an introduction to the aldol, Claisen, and Michael reactions, all three of which are important means for the formation of new carbon–carbon bonds. Chapter 16 provides a brief introduction to organic polymer chemistry.

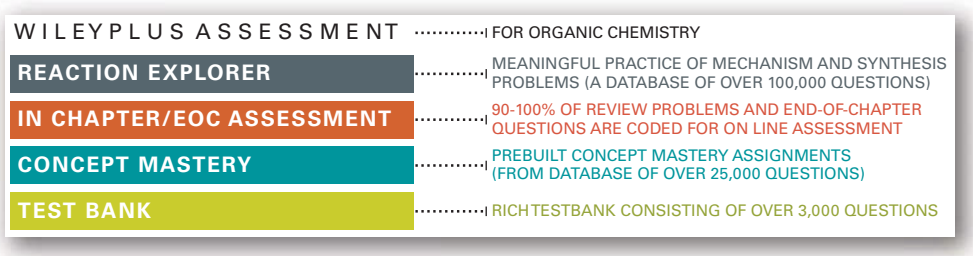
Chapters 17–20 present an introduction to the organic chemistry of carbohydrates; amino acids and proteins; nucleic acids; and lipids. Chapter 21, The Organic Chemistry of Metabolism, demonstrates how the chemistry developed to this point can be applied to an understanding of three major metabolic pathways—glycolysis, the β-oxidation of fatty acids, and the citric acid cycle.

WileyPLUS for Organic Chemistry

What do students receive with WileyPLUS?

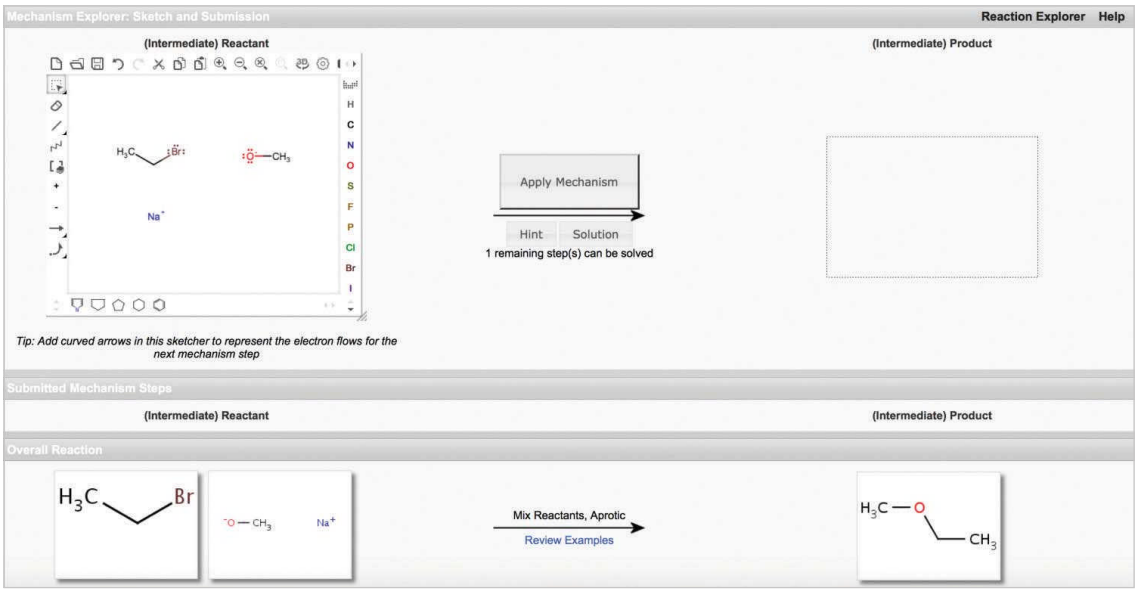
- The complete digital textbook, saving students up to 60% off the cost of the printed text.
- Question assistance, including links to relevant sections in the online digital textbook.
- Immediate feedback and proof of progress, 24/7.
- Integrated, multi-media resources that address your students' unique learning styles, levels of proficiency, and levels of preparation by providing multiple study paths and encourage more active learning.

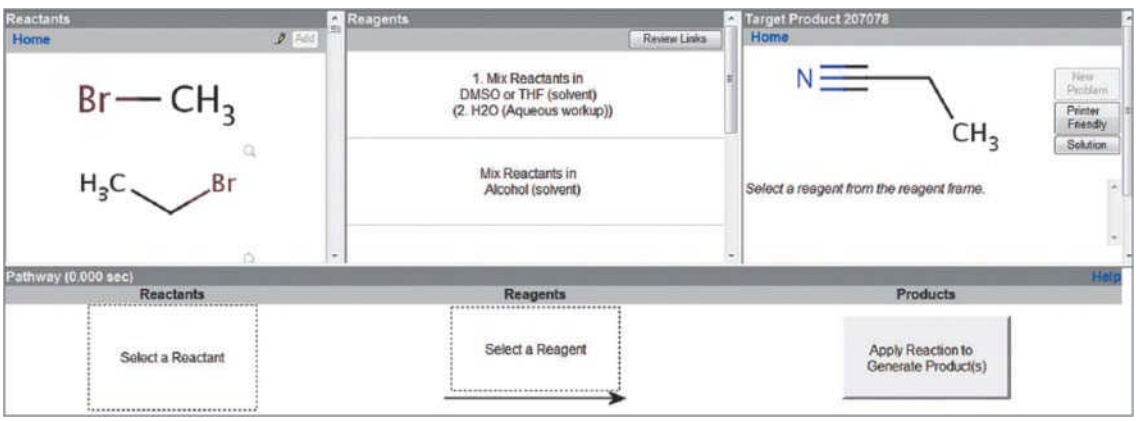
Four unique silos of assessment are available to instructors for creating online homework and quizzes and are designed to enable and support problem-solving skill development and conceptual understanding:

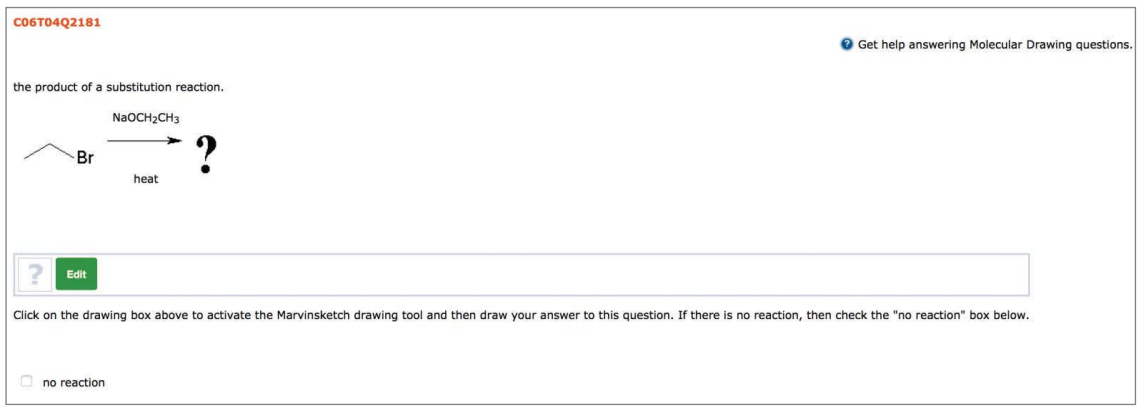


Reaction Explorer—Students' ability to understand mechanisms and predict synthesis reactions greatly impacts their level of success in the course. **Reaction Explorer** is an interactive system for **learning and practicing reactions**, **syntheses**, and **mechanisms** in organic chemistry with advanced support for the automatic generation of random problems and curved arrow mechanism diagrams.

Mechanism Explorer provides valuable practice of reactions and mechanisms.







Synthesis Explorer provides meaningful practice of single and multistep synthesis.
End-of-Chapter Problems—A subset of the end-of-chapter problems is included for use in *WileyPLUS*. Many of the problems are algorithmic and feature structure drawing/assessment functionality using MarvinSketch, with immediate answer feedback.

Prebuilt Concept Mastery Assignments—Students must continuously practice and work organic chemistry problems in order to master the concepts and skills presented in the course. **Prebuilt concept mastery assignments** offer students ample opportunities for practice in each chapter. Each assignment is organized by topic and features feedback for incorrect answers.

These assignments pull from a unique database of over 25,000 questions, over half of which require students to draw a structure using MarvinSketch.
Test Bank—A robust Test Bank, containing over 2,000 questions, is also available within *WileyPLUS* as an additional resource for creating assignments or tests.

With WileyPLUS, students receive:

- **Key Concept Videos**
- **Chapter Zero: General Chemistry Refresher**: To ensure that students have mastered the necessary prerequisite content from General Chemistry, *WileyPLUS* includes a complete chapter of core General Chemistry topics with corresponding assignments.
- **Office Hour Videos, Solved Problem Videos, and Video Mini-Lectures:** In each chapter, several types of video assistance are included to help students with conceptual understanding and problem-solving strategies. The video mini-lectures focus on challenging concepts; the Office Hours videos take these concepts and apply them to example problems, emulating the experience that a student would get if she or he were to attend office hours and ask for assistance in working a problem. The Solved Problem videos use the solved problems from the book, audio, and a whiteboard. The goal is to illustrate good problem solving strategies.
- **Skill-Building Exercises** that utilize animated exercises, with instant feedback, to reinforce the key skills required to succeed in organic chemistry
- **3D Visualization Animations** that use the latest visual and audio technologies to help students understnd concepts. Instructors can assign quizzes based on these visualizations in *WileyPLUS*

With WileyPLUS, instructors receive:

- QuickStart
- Four unique silos of assessment for creating online homework and quizzes
- Reliable resources that reinforce course goals inside and outside of the classroom

- The ability to easily identify those students who are falling behind by tracking their progress and offering assistance early, even before they come to office hours. *WileyPLUS* simplifies and automates such tasks as student performance assessment, creating assignments, scoring student work, keeping grades, and more.
- Media-rich course materials and assessment content that allow customization of the classroom presentation with a wealth of resources and functionality from PowerPoint slides to a database of rich visuals.

Support Package for Students

Student Solutions Manual: Authored by Felix Lee, of The University of Western Ontario, and reviewed by Professors Brown and Poon. The Student Solutions Manual contains detailed solutions to all problems, including the Quick Quiz questions and the Putting It Together questions.

Support Package for Instructors

All Instructor Resources are available within *WileyPLUS* or they can be accessed by contacting your local Wiley Sales Representative.
PowerPoint Presentations: Authored by William Brown, the PPT lecture slides provide a pre-built set of approximately 700 slides corresponding to every chapter in the text. The slides include examples and illustrations that help reinforce and test students' grasp of organic chemistry concepts. An additional set of PPT slides, featuring the illustrations, figures, and tables from the text, are also available. All PPT slide presentations are customizable to fit your course.
Test Bank: Authored by Stefan Bossmann of Kansas State University, the Test Bank for this edition has been revised and updated to include over 2,000 short-answer, multiple-choice, and true-false questions. It is available in both printed and computerized versions.
Digital Image Library: Images from the text are available online in JPEG format. Instructors may use these to customize their presentations and to provide additional visual support for quizzes and exams.

Acknowledgments

While one or a few persons are listed as "authors" of any textbook, the book is in fact the product of collaboration of many individuals, some obvious and some not so obvious. It is with gratitude that we acknowledge the contributions of the many. We begin with Felix Lee, who has worked with us for so many years on both the solutions manual and the solutions to problems in all parts of the text. His keen eye and chemical expertise has helped to improve this edition in so many ways. A special thanks go to Professor Robert White of Dalhousie University for taking the time to inform us of errors that he found in the previous edition. We also thank Senior Production Editor Patty Donovan at SPi Global for her incredible organizational skills and patience. Speaking of patience, the entire Wiley production and editorial team is to be commended for their patience, skill and professionalism on this project including Joan Kakut, Chemistry Development Editor; Alyson Rentrop, Associate Development Editor, Mallory Fryc, Chemistry Editorial Assistant; Sandra Dumas, Senior Production Editor, and Wendy Lai, Senior Graphic Designer, for her creative contributions to the covers of both this and the previous edition of the text. We thank Sophia Brown for a student's eye view of the PowerPoint Lecture series. Finally, we thank all our students, both past and present, for their many positive interactions over the years that have guided us in creating this textbook.

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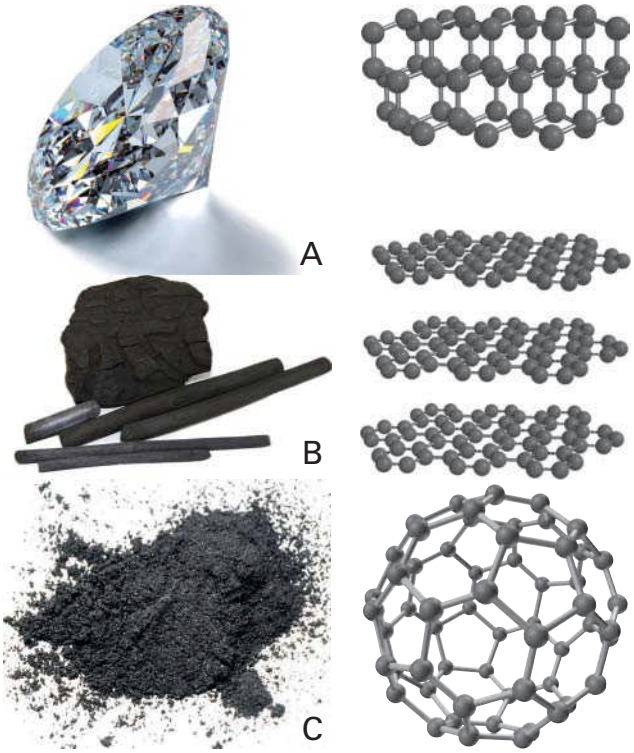

(A) James Steidl/Shutterstock, (B) PortiadeCastro/Getty Images, Inc.
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Covalent Bonding and Shapes of Molecules

Three forms of elemental carbon, (A) diamond, (B) graphite, and (C) buckminsterfullerene, along with their molecular models. Notice how vastly different their molecular structures are with diamond having an interconnected network of atoms, graphite existing as sheets, and buckminsterfullerene's atoms arranged like a soccer ball.

1

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

WHAT DO THE FOODS THAT WE EAT, the fragrances that we smell, the medicines that we take, the tissues that make up all living things, the fuels that we burn, and the many products that constitute our modern conveniences in life have in common? They all contain **organic compounds**, compounds that consist of at least one carbon and oftentimes other elements such as hydrogen, oxygen, nitrogen, sulfur, and others from the Periodic Table. The study of these compounds is known as **organic chemistry**.

Organic chemistry The study of the chemical and physical properties of the compounds of carbon.

You are about to embark on an exploration of organic chemistry, which spans a large majority of the roughly 88 million chemical substances that have been cataloged. How can one book cover the chemistry of tens of millions of compounds? It turns out that elements commonly arrange themselves in ways that are predictable and that consistently exhibit similar properties. In this chapter, we review how these arrangements of elements such as carbon, hydrogen, oxygen, and nitrogen are achieved through the sharing of electrons to form molecules. We will then learn chemical trends found in these arrangements and use this knowledge to make our study of organic chemistry manageable and fun.

1.1 How Do We Describe the Electronic Structure of Atoms?

You are already familiar with the fundamentals of the electronic structure of atoms from a previous study of chemistry. Briefly, an atom contains a small, dense nucleus made of neutrons and positively charged protons (Figure 1.1a).

Shells A region of space around a nucleus where electrons are found.

Electrons do not move freely in the space around a nucleus, but rather are confined to regions of space called **principal energy levels** or, more simply, **shells**. We number these shells 1, 2, 3, and so forth from the inside out (Figure 1.1b).

Orbital A region of space where an electron or pair of electrons spends 90 to 95% of its time.

Shells are divided into subshells designated by the letters *s*, *p*, *d*, and *f*, and within these subshells, electrons are grouped in orbitals (Table 1.1). An **orbital** is a region of space that can hold 2 electrons. In this course, we focus on compounds of carbon with hydrogen, oxygen, and nitrogen, all of which use only electrons in *s* and *p* orbitals for covalent bonding. Therefore, we are concerned primarily with *s* and *p* orbitals.

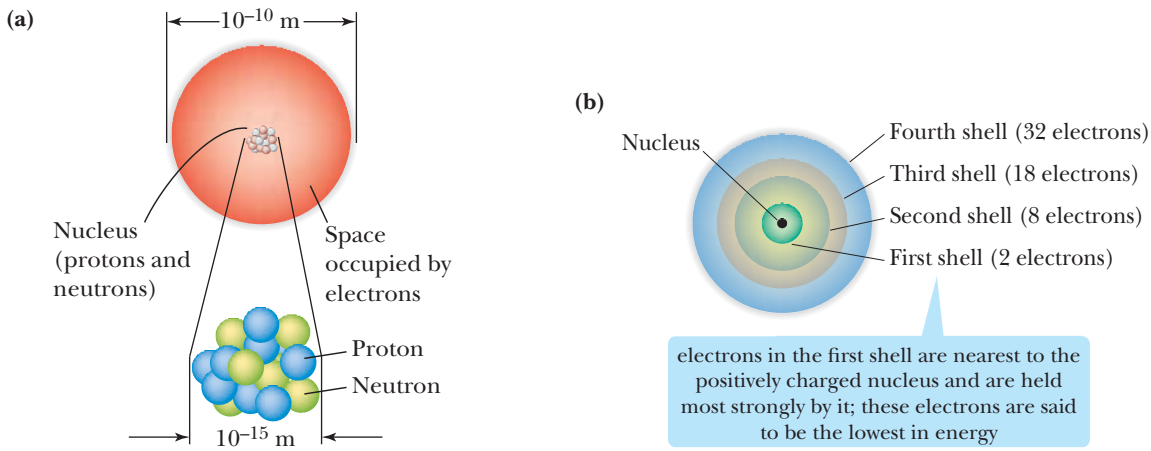


FIGURE 1.1 A schematic view of an atom. (a) Most of the mass of an atom is concentrated in its small, dense nucleus, which has a diameter of 10^{-14} to 10^{-15} meter (m). (b) Each shell can contain up to $2n^2$ electrons, where n is the number of the shell. Thus, the first shell can hold 2 electrons, the second 8 electrons, the third 18, the fourth 32, and so on (Table 1.1).

the first shell contains a single orbital called a 1*s* orbital. The second shell contains one 2*s* orbital and three 2*p* orbitals. All *p* orbitals come in sets of three and can hold up to 6 electrons. The third shell contains one 3*s* orbital, three 3*p* orbitals, and five 3*d* orbitals. All *d* orbitals come in sets of five and can hold up to 10 electrons. All *f* orbitals come in sets of seven and can hold up to 14 electrons

TABLE 1.1 Distribution of Orbitals within Shells

Shell	Orbitals Contained in Each Shell	Maximum Number of Electrons Shell Can Hold	Relative Energies of Electrons in Each Shell
4	One 4*s*, three 4*p*, five 4*d*, and seven 4*f* orbitals	2 + 6 + 10 + 14 = 32	Higher
3	One 3*s*, three 3*p*, and five 3*d* orbitals	2 + 6 + 10 = 18	
2	One 2*s* and three 2*p* orbitals	2 + 6 = 8	
1	One 1*s* orbital	2	Lower

A. Electron Configuration of Atoms

Ground-state electron configuration The electron configuration of lowest energy for an atom, molecule, or ion.

The electron configuration of an atom is a description of the orbitals the electrons in the atom occupy. Every atom has an infinite number of possible electron configurations. At this stage, we are concerned only with the **ground-state electron configuration**—the electron configuration of lowest energy. Table 1.2 shows ground-state electron configurations

TABLE 1.2 Ground-State Electron Configurations for Elements 1–18*

First Period	H	1	$1s^1$	
	He	2	$1s^2$	
Second Period	Li	3	$1s^2s^1$	[He] $2s^1$
	Be	4	$1s^22s^2$	[He] $2s^2$
	B	5	$1s^22s^22p_x^1$	[He] $2s^22p_x^1$
	C	6	$1s^22s^22p_x^12p_y^1$	[He] $2s^22p_x^12p_y^1$
	N	7	$1s^22s^22p_x^12p_y^12p_z^1$	[He] $2s^22p_x^12p_y^12p_z^1$
	O	8	$1s^22s^22p_x^22p_y^12p_z^1$	[He] $2s^22p_x^22p_y^12p_z^1$
	F	9	$1s^22s^22p_x^22p_y^22p_z^1$	[He] $2s^22p_x^22p_y^22p_z^1$
	Ne	10	$1s^22s^22p_x^22p_y^22p_z^2$	[He] $2s^22p_x^22p_y^22p_z^2$
Third Period	Na	11	$1s^22s^22p_x^22p_y^22p_z^23s^1$	[Ne] $3s^1$
	Mg	12	$1s^22s^22p_x^22p_y^22p_z^23s^2$	[Ne] $3s^2$
	Al	13	$1s^22s^22p_x^22p_y^22p_z^23s^23p_x^1$	[Ne] $3s^23p_x^1$
	Si	14	$1s^22s^22p_x^22p_y^22p_z^23s^23p_x^13p_y^1$	[Ne] $3s^23p_x^13p_y^1$
	P	15	$1s^22s^22p_x^22p_y^22p_z^23s^23p_x^13p_y^13p_z^1$	[Ne] $3s^23p_x^13p_y^13p_z^1$
	S	16	$1s^22s^22p_x^22p_y^22p_z^23s^23p_x^23p_y^13p_z^1$	[Ne] $3s^23p_x^23p_y^13p_z^1$
	Cl	17	$1s^22s^22p_x^22p_y^22p_z^23s^23p_x^23p_y^23p_z^1$	[Ne] $3s^23p_x^23p_y^23p_z^1$
	Ar	18	$1s^22s^22p_x^22p_y^22p_z^23s^23p_x^23p_y^23p_z^2$	[Ne] $3s^23p_x^23p_y^23p_z^2$

*Elements are listed by symbol, atomic number, ground-state electron configuration, and shorthand notation for the ground-state electron configuration, in that order.

Rule 1. Orbitals in these elements fill in the order 1*s*, 2*s*, 2*p*, 3*s*, and 3*p*.

Rule 2. Notice that each orbital contains a maximum of two electrons. In neon, there are six additional electrons after the 1*s* and 2*s* orbitals are filled. These are written as $2p_x^2 2p_y^2 2p_z^2$. Alternatively, we can group the three filled 2*p* orbitals and write them in a condensed form as $2p^6$.

Rule 3. Because the p_x, p_y, and p_z orbitals are equal in energy, we fill each with one electron before adding a second electron. That is, only after each 3*p* orbital contains one electron do we add a second electron to the $3p_x$ orbital.

for the first 18 elements of the Periodic Table. We determine the ground-state electron configuration of an atom with the use of the following three rules:

Rule 1. *Orbitals fill in order of increasing energy from lowest to highest* (Figure 1.2).

Rule 2. *Each orbital can hold up to two electrons with their spins paired. Spin pairing* means that each electron spins in a direction opposite that of its partner (Figure 1.3). We show this pairing by writing two arrows, one with its head up and the other with its head down.

Rule 3. *When orbitals of equivalent energy are available, but there are not enough electrons to fill them completely, then we add one electron to each equivalent orbital before we add a second electron to any one of them.*

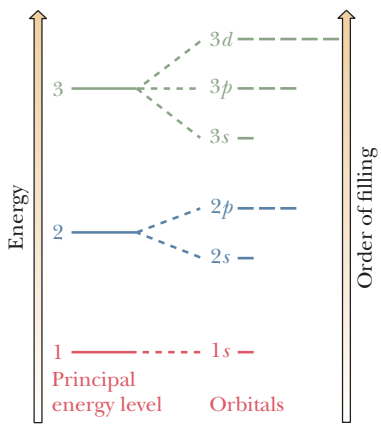


FIGURE 1.2 Relative energies and order of filling of orbitals through the 3*d* orbitals.

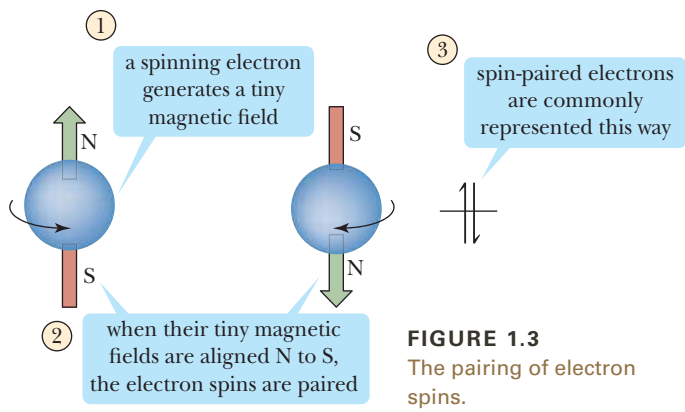


FIGURE 1.3 The pairing of electron spins.

B. Lewis Structures

In discussing the physical and chemical properties of an element, chemists often focus on the outermost shell of its atoms, because electrons in this shell are the ones involved in the formation of chemical bonds and in chemical reactions. We call outer-shell electrons **valence electrons**, and we call the energy level in which they are found the **valence shell**. Carbon, for example, with a ground-state electron configuration of $1s^22s^22p^2$, has four valence (outer-shell) electrons.

Valence electrons Electrons in the valence (outermost) shell of an atom.

Valence shell The outermost electron shell of an atom.

EXAMPLE 1.1

Write ground-state electron configurations for these elements:
(a) Lithium **(b)** Oxygen **(c)** Chlorine

STRATEGY

Locate each atom in the Periodic Table and determine its atomic number. The order of filling of orbitals is 1*s*, 2*s*, $2p_x$, $2p_y$, $2p_z$, and so on.

SOLUTION

(a) Lithium (atomic number 3): $1s^2 2s^1$. Alternatively, we can write the ground-state electron configuration as [He] $2s^1$.

(b) Oxygen (atomic number 8): $1s^2 2s^2 2p_x^2 2p_y^1 2p_z^1$. Alternatively, we can group the four electrons of the 2*p* orbitals together and write the ground-state electron configuration as $1s^2 2s^2 2p^4$. We can also write it as [He] $2s^2 2p^4$.

(c) Chlorine (atomic number 17): $1s^2 2s^2 2p^6 3s^2 3p^5$. Alternatively, we can write it as [Ne] $3s^2 3p^5$.

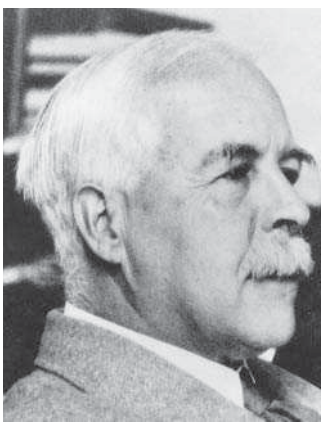
See problems 1.17–1.20

PROBLEM 1.1

Write and compare the ground-state electron configurations for the elements in each set. What can be said about the outermost shell of orbitals for each pair of elements?

(a) Carbon and silicon
(b) Oxygen and sulfur
(c) Nitrogen and phosphorus

Lewis structure of an atom The symbol of an element surrounded by a number of dots equal to the number of electrons in the valence shell of the atom.



UPI/© Corbis

Gilbert N. Lewis (1875–1946) introduced the theory of the electron pair that extended our understanding of covalent bonding and of the concept of acids and bases. It is in his honor that we often refer to an "electron dot" structure as a Lewis structure.

To show the outermost electrons of an atom, we commonly use a representation called a **Lewis structure**, after the American chemist Gilbert N. Lewis (1875–1946), who devised this notation. A Lewis structure shows the symbol of the element, surrounded by a number of dots equal to the number of electrons in the outer shell of an atom of that element. In Lewis structures, the atomic symbol represents the nucleus and all filled inner shells. Table 1.3 shows Lewis structures for the first 18 elements of the Periodic Table. As you study the entries in the table, note that, with the exception of helium, the number of valence electrons of the element corresponds to the group number of the element in the Periodic Table; for example, oxygen, with six valence electrons, is in Group 6A.

At this point, we must say a word about the numbering of the columns (families or groups) in the Periodic Table. Dmitri Mendeleev gave them numerals and added the letter A for some columns and B for others. This pattern remains in common use in the United States today. In 1985, however, the International Union of Pure and Applied Chemistry (IUPAC) recommended an alternative system in which the columns are numbered 1 to 18 beginning on the left and without added letters. Although we use the original Mendeleev system in this text, the Periodic Table at the front of the text shows both.

Notice from Table 1.3 that, because of the differences in number and kind of valence shell orbitals available to elements of the second and third periods, significant differences exist in the covalent bonding of oxygen and sulfur and of nitrogen and phosphorus. For example, although oxygen and nitrogen can accommodate no more than 8 electrons in their valence shells, many phosphorus-containing compounds have 10 electrons in the valence shell of phosphorus, and many sulfur-containing compounds have 10 and even 12 electrons in the valence shell of sulfur.

the valence shell of 1st period elements contain only *s* orbitals

the valence shell of 2nd period elements contains *s* and *p* orbitals

TABLE 1.3 Lewis Structures for Elements 1–18 of the Periodic Table

1A	2A	3A	4A	5A	6A	7A	8A
H·							He:
Li·	Be:	B:	·C:	·N:	:O:	:F:	:Ne:
Na·	Mg:	Al:	·Si:	·P:	:S:	:Cl:	:Ar:

the valence shell of 3rd period elements contains *s*, *p*, and *d* orbitals. The *d* orbitals allow for expanded covalent bonding opportunities for 3rd period elements

1.2 What Is the Lewis Model of Bonding?

A. Formation of Ions

In 1916, Lewis devised a beautifully simple model that unified many of the observations about chemical bonding and reactions of the elements. He pointed out that the chemical inertness of the noble gases (Group 8A) indicates a high degree of stability of the electron configurations of these elements: helium with a valence shell of two electrons ($1s^2$), neon with a valence shell of eight electrons ($2s^2 2p^6$), argon with a valence shell of eight electrons ($3s^2 3p^6$), and so forth.

Noble Gas	Noble Gas Notation
He	$1s^2$
Ne	[He] $2s^2 2p^6$
Ar	[Ne] $3s^2 3p^6$
Kr	[Ar] $4s^2 4p^6 3d^{10}$
Xe	[Kr] $5s^2 5p^6 4d^{10}$

The tendency of atoms to react in ways that achieve an outer shell of eight valence electrons is particularly common among elements of Groups 1A–7A (the main-group elements). We give this tendency the special name, the **octet rule**. An atom with almost eight valence electrons tends to gain the needed electrons to have eight electrons in its valence shell and an electron configuration like that of the noble gas nearest it in atomic number. In gaining electrons, the atom becomes a negatively charged ion called an **anion**. An atom with only one or two valence electrons tends to lose the number of electrons required to have the same electron configuration as the noble gas nearest it in atomic number. In losing one or more electrons, the atom becomes a positively charged ion called a **cation**.

Octet rule The tendency among atoms of Group 1A–7A elements to react in ways that achieve an outer shell of eight valence electrons.

Anion An atom or group of atoms bearing a negative charge.

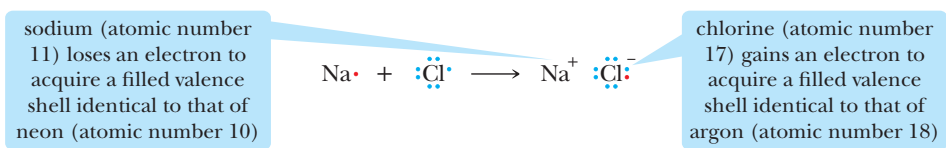
Cation An atom or group of atoms bearing a positive charge.

B. Formation of Chemical Bonds

According to the Lewis model of bonding, atoms interact with each other in such a way that each atom participating in a chemical bond acquires a valence-shell electron configuration the same as that of the noble gas closest to it in atomic number. Atoms acquire completed valence shells in two ways:

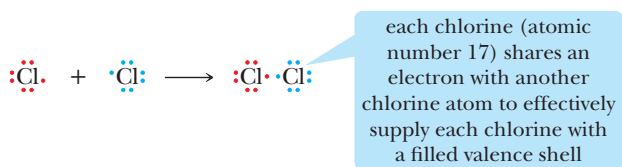
1. An atom may lose or gain enough electrons to acquire a filled valence shell. An atom that gains electrons becomes an anion, and an atom that loses electrons becomes a cation. A chemical bond between an anion and a cation is called an **ionic bond**.

Ionic bond A chemical bond resulting from the electrostatic attraction of an anion and a cation.



2. An atom may share electrons with one or more other atoms to acquire a filled valence shell. A chemical bond formed by sharing electrons is called a **covalent bond**.

Covalent bond A chemical bond resulting from the sharing of one or more pairs of electrons.



We now ask how we can find out whether two atoms in a compound are joined by an ionic bond or a covalent bond. One way to answer this question is to consider the relative positions of the two atoms in the Periodic Table. Ionic bonds usually form between a metal and a nonmetal. An example of an ionic bond is that formed between the metal sodium and the nonmetal chlorine in the compound sodium chloride, Na^+Cl^-. By contrast, when two nonmetals or a metalloid and a nonmetal combine, the bond between them is usually covalent. Examples of compounds containing covalent bonds between nonmetals include Cl_2, H_2O, CH_4, and NH_3. Examples of compounds containing covalent bonds between a metalloid and a nonmetal include BF_3, $SiCl_4$, and AsH_4.

EXAMPLE 1.2

Show how the loss of one electron from a sodium atom to form a sodium ion leads to a stable octet:

$$\underset{\text{A sodium atom}}{Na} \longrightarrow \underset{\text{A sodium ion}}{Na^+} + \underset{\text{An electron}}{e^-}$$

STRATEGY

To see how this chemical change leads to a stable octet, write the condensed ground-state electron configuration for a sodium atom and for a sodium ion, and then compare the two to the noble gas nearest to sodium in atomic number.

SOLUTION

A sodium atom has one electron in its valence shell. The loss of this one valence electron changes the sodium atom to a sodium ion, Na^+, which has a complete octet of electrons in its valence shell and the same electron configuration as neon, the noble gas nearest to it in atomic number.

Na (11 electrons): $1s^2 2s^2 2p^6 3s^1$

Na^+ (10 electrons): $1s^2 2s^2 2p^6$

Ne (10 electrons): $1s^2 2s^2 2p^6$

See problems 1.22, 1.23

PROBLEM 1.2

Show how the gain of two electrons by a sulfur atom to form a sulfide ion leads to a stable octet:

$$S + 2e^- \longrightarrow S^{2-}$$

Another way to identify the type of bond is to compare the electronegativities of the atoms involved, which is the subject of the next subsection.

C. Electronegativity and Chemical Bonds

Electronegativity A measure of the force of an atom's attraction for electrons it shares in a chemical bond with another atom.

Electronegativity is a measure of the force of an atom's attraction for electrons that it shares in a chemical bond with another atom. The most widely used scale of electronegativities (Table 1.4) was devised by Linus Pauling in the 1930s. On the Pauling scale, fluorine, the most electronegative element, is assigned an electronegativity of 4.0, and all other elements are assigned values in relation to fluorine.

As you study the electronegativity values in this table, note that they generally increase from left to right within a period of the Periodic Table and generally increase from bottom to top within a group. Values increase from left to right because of the increasing positive charge on the nucleus, which leads to a stronger attraction for electrons in the valence shell. Values increase going up a column because of the decreasing distance of the valence electrons from the nucleus, which leads to stronger attraction between a nucleus and its valence electrons.

Note that the values given in Table 1.4 are only approximate. The electronegativity of a particular element depends not only on its position in the Periodic Table, but also on its oxidation state. The electronegativity of Cu(I) in Cu_2O, for example, is 1.8, whereas the electronegativity of Cu(II) in CuO is 2.0. In spite of these variations, electronegativity is still a useful guide to the distribution of electrons in a chemical bond.

UPI/© Corbis

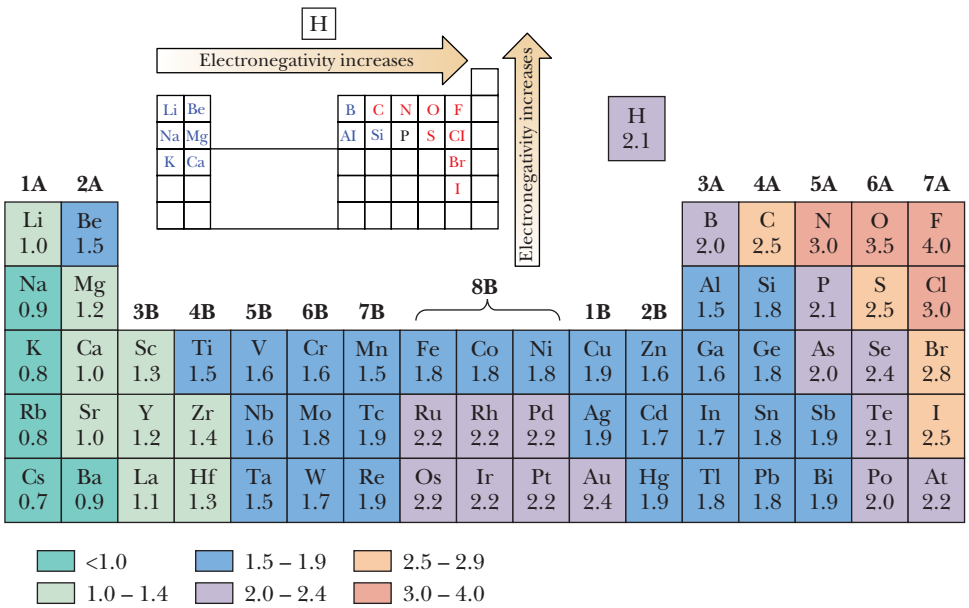
Linus Pauling (1901–1994) was the first person ever to receive two unshared Nobel Prizes. He received the Nobel Prize for Chemistry in 1954 for his contributions to the nature of chemical bonding. He received the Nobel Prize for Peace in 1962 for his efforts on behalf of international control of nuclear weapons and against nuclear testing.

Ionic Bonds

An ionic bond forms by the transfer of electrons from the valence shell of an atom of lower electronegativity to the valence shell of an atom of higher electronegativity. The more electronegative atom gains one or more valence electrons and becomes an anion; the less electronegative atom loses one or more valence electrons and becomes a cation.

As a guideline, we say that this type of electron transfer to form an ionic compound is most likely to occur if the difference in electronegativity between two atoms is approximately 1.9 or greater. A bond is more likely to be covalent if this difference is less than 1.9. Note that the value 1.9 is somewhat arbitrary: Some chemists prefer a slightly larger value, others a slightly smaller value. The essential point is that the value 1.9 gives us a guidepost against which to decide whether a bond is more likely to be ionic or more likely to be covalent.

TABLE 1.4 Electronegativity Values and Trends for Some Atoms (Pauling Scale)



Partial Periodic Table showing commonly encountered elements in organic chemistry. Electronegativity generally increases from left to right within a period and from bottom to top within a group. Hydrogen is less electronegative than the elements in red and more electronegative than those in blue. Hydrogen and phosphorus have the same electronegativity on the Pauling scale.

An example of an ionic bond is that formed between sodium (electronegativity 0.9) and fluorine (electronegativity 4.0). The difference in electronegativity between these two elements is 3.1. In forming Na^+F^-, the single $3s$ valence electron of sodium is transferred to the partially filled valence shell of fluorine:

$$Na(1s^2\,2s^2\,2p^6\,\boxed{3s^1}) + F(1s^2\,2s^2\,\boxed{2p^5}) \longrightarrow Na^+(1s^2 2s^2 2p^6) + F^-(1s^2 2s^2\,\boxed{2p^6})$$

As a result of this transfer of one electron, both sodium and fluorine form ions that have the same electron configuration as neon, the noble gas closest to each in atomic number. In the following equation, we use a single-headed curved arrow to show the transfer of one electron from sodium to fluorine:

EXAMPLE 1.3

Judging from their relative positions in the Periodic Table, which element in each pair has the larger electronegativity?

(a) Lithium or carbon
(b) Nitrogen or oxygen
(c) Carbon or oxygen

STRATEGY

Determine whether the pair resides in the same period (row) or group (column) of the Periodic Table. For those in the same period, electronegativity increases from left to right. For those in the same group, electronegativity increases from bottom to top.

SOLUTION

The elements in these pairs are all in the second period of the Periodic Table. Electronegativity in this period increases from left to right.

(a) C > Li
(b) O > N
(c) O > C

See problem 1.24

PROBLEM 1.3

Judging from their relative positions in the Periodic Table, which element in each pair has the larger electronegativity?

(a) Lithium or potassium
(b) Nitrogen or phosphorus
(c) Carbon or silicon
(d) Oxygen or phosphorus
(e) Oxygen or silicon

Covalent Bonds

A covalent bond forms when electron pairs are shared between two atoms whose difference in electronegativity is 1.9 or less. According to the Lewis model, an electron pair in a covalent bond functions in two ways simultaneously: It is shared by two atoms, and, at the same time, it fills the valence shell of each atom.

The simplest example of a covalent bond is that in a hydrogen molecule, H_2. When two hydrogen atoms bond, the single electrons from each atom combine to form an electron pair with the release of energy. A bond formed by sharing a pair of electrons is called a *single bond* and is represented by a single line between the two atoms. The electron pair shared between the two hydrogen atoms in H_2 completes the valence shell of each hydrogen. Thus, in H_2, each hydrogen has two electrons in its valence shell and an electron configuration like that of helium, the noble gas nearest to it in atomic number:

$$H\cdot + \cdot H \rightarrow H{-}H \qquad \Delta H^0 = -435 \text{ kJ / mol } (-104 \text{ kcal / mol})$$

The Lewis model accounts for the stability of covalently bonded atoms in the following way: In forming a covalent bond, an electron pair occupies the region between two nuclei and serves to shield one positively charged nucleus from the repulsive force of the other positively charged nucleus. At the same time, an electron pair attracts both nuclei. In other words, an electron pair in the space between two nuclei bonds them together and fixes the internuclear distance to within very narrow limits. The distance between nuclei participating in a chemical bond is called a **bond length**. Every covalent bond has a definite bond length. In H—H, it is 74 pm, where 1 pm = 10^{-12} m.

Although all covalent bonds involve the sharing of electrons, they differ widely in the degree of sharing. We classify covalent bonds into two categories—nonpolar covalent and polar covalent—depending on the difference in electronegativity between the bonded atoms. In a **nonpolar covalent bond**, electrons are shared equally. In a **polar covalent bond**, they are shared unequally. It is important to realize that no sharp line divides these two categories, nor, for that matter, does a sharp line divide polar covalent bonds and ionic bonds. Nonetheless, the rule-of-thumb guidelines in Table 1.5 will help you decide whether a given bond is more likely to be nonpolar covalent, polar covalent, or ionic.

Nonpolar covalent bond A covalent bond between atoms whose difference in electronegativity is less than approximately 0.5.

Polar covalent bond A covalent bond between atoms whose difference in electronegativity is between approximately 0.5 and 1.9.

A covalent bond between carbon and hydrogen, for example, is classified as non-polar covalent because the difference in electronegativity between these two atoms is 2.5 − 2.1 = 0.4 unit. An example of a polar covalent bond is that of H—Cl. The difference in electronegativity between chlorine and hydrogen is 3.0 − 2.1 = 0.9 unit.

An important consequence of the unequal sharing of electrons in a polar covalent bond is that the more electronegative atom gains a greater fraction of the shared electrons and acquires a partial negative charge, which we indicate by the symbol $\delta-$ (read "delta minus"). The less electronegative atom has a lesser fraction of the shared electrons and acquires a partial positive charge, which we indicate by the symbol $\delta+$ (read "delta plus"). This separation of charge produces a **dipole** (two poles). We can also show the presence of a bond dipole by an arrow, with the head of the arrow near the negative end of the dipole and a cross on the tail of the arrow near the positive end (Figure 1.4).

We can display the polarity of a covalent bond by a type of molecular model called an *electron density model*. In this type of model, a blue color shows the presence of a $\delta+$ charge, and a red color shows the presence of a $\delta-$ charge. Figure 1.4 shows an electron density model of HCl. The ball-and-stick model in the center shows the orientation of the two atoms in space. The transparent surface surrounding the ball-and-stick model shows the relative sizes of the atoms (equivalent to the size shown by a space-filling model). Colors on

TABLE 1.5 Classification of Chemical Bonds

Difference in Electronegativity between Bonded Atoms	Type of Bond	Most Likely Formed Between
Less than 0.5	Nonpolar covalent	Two nonmetals or a nonmetal and a metalloid
0.5 to 1.9	Polar covalent	
Greater than 1.9	Ionic	A metal and a nonmetal

EXAMPLE 1.4

Classify each bond as nonpolar covalent, polar covalent, or ionic:

(a) O—H
(b) N—H
(c) Na—F
(d) C—Mg

STRATEGY

Use the difference in electronegativity between the two atoms and compare this value with the range of values given in Table 1.5.

SOLUTION

On the basis of differences in electronegativity between the bonded atoms, three of these bonds are polar covalent and one is ionic:

Bond	Difference in Electronegativity	Type of Bond
(a) O—H	3.5 – 2.1 = 1.4	polar covalent
(b) N—H	3.0 – 2.1 = 0.9	polar covalent
(c) Na—F	4.0 – 0.9 = 3.1	ionic
(d) C—Mg	2.5 – 1.2 = 1.3	polar covalent

See problem 1.25

PROBLEM 1.4

Classify each bond as nonpolar covalent, polar covalent, or ionic:
(a) S—H **(b)** P—H **(c)** C—F **(d)** C—Cl

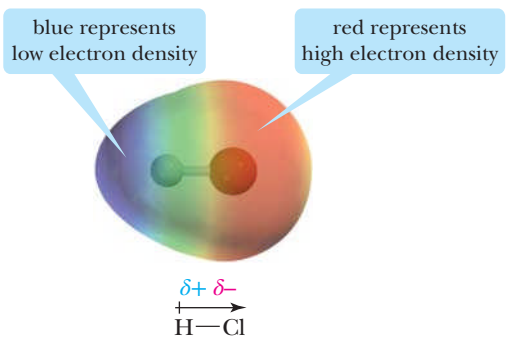


FIGURE 1.4 An electron density model of HCl. Red indicates a region of high electron density, and blue indicates a region of low electron density.

the surface show the distribution of electron density. We see by the blue color that hydrogen bears a $\delta+$ charge and by the red color that chlorine bears a $\delta-$ charge.

In summary, the twin concepts of electronegativity and the polarity of covalent bonds will be very helpful in organic chemistry as a guide to locating centers of chemical reactions. In many of the reactions we will study, reaction is initiated by the attraction between a center of partial positive charge and a center of partial negative charge.

From the study of the compounds in Table 1.6 and other organic compounds, we can make the following generalizations: In neutral (uncharged) organic compounds,

- H has one bond.
- C has four bonds.
- N has three bonds and one unshared pair of electrons.
- O has two bonds and two unshared pair of electrons.
- F, Cl, Br, and I have one bond and three unshared pairs of electrons.

D. Formal Charge

Throughout this course, we deal not only with molecules, but also with polyatomic cations and polyatomic anions. Examples of polyatomic cations are the hydronium ion, H_3O^+, and the ammonium ion, NH_4^+. An example of a polyatomic anion is the bicarbonate ion, HCO_3^-.

EXAMPLE 1.5

Using a bond dipole arrow and the symbols $\delta-$ and $\delta+$, indicate the direction of polarity in these polar covalent bonds:

(a) C—O **(b)** N—H **(c)** C—Mg

STRATEGY

To determine the polarity of a covalent bond and the direction of the polarity, compare the electronegativities of the bonded atoms. Remember that a bond dipole arrow always points toward the more electronegative atom.

SOLUTION

For (a), carbon and oxygen are both in period 2 of the Periodic Table. Because oxygen is farther to the right than carbon, it is more electronegative. For (b), nitrogen is more electronegative than hydrogen. For (c), magnesium is a metal located at the far left of the Periodic Table, and carbon is a nonmetal located at the right. All nonmetals, including hydrogen, have a greater electronegativity than do the metals in columns 1A and 2A. The electronegativity of each element is given below the symbol of the element:

(a) $\overset{\delta+}{\underset{2.5}{C}}—\overset{\delta-}{\underset{3.5}{O}}$ **(b)** $\overset{\delta-}{\underset{3.0}{N}}—\overset{\delta+}{\underset{2.1}{H}}$ **(c)** $\overset{\delta-}{\underset{2.5}{C}}—\overset{\delta+}{\underset{1.2}{Mg}}$

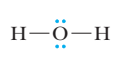
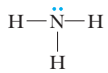
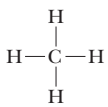
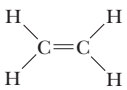
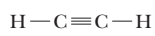
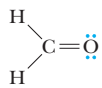
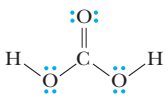
See problems 1.26, 1.38, 1.40

PROBLEM 1.5

Using a bond dipole arrow and the symbols $\delta-$ and $\delta+$, indicate the direction of polarity in these polar covalent bonds:

(a) C—N **(b)** N—O **(c)** C—Cl

TABLE 1.6 Lewis Structures for Several Molecules. The number of valence electrons in each molecule is given in parentheses after the molecule's molecular formula

 H_2O (8) Water	 NH_3 (8) Ammonia	 CH_4 (8) Methane	 HCl (8) Hydrogen chloride
 C_2H_4 (12) Ethylene	 C_2H_2 (10) Acetylene	 CH_2O (12) Formaldehyde	 H_2CO_3 (24) Carbonic acid

Formal charge The charge on an atom in a molecule or polyatomic ion.

Nonbonding electrons Valence electrons not involved in forming covalent bonds, that is, unshared electrons.

Bonding electrons Valence electrons shared in a covalent bond.

It is important that you be able to determine which atom or atoms in a molecule or polyatomic ion bear the positive or negative charge. The charge on an atom in a molecule or polyatomic ion is called its **formal charge**. To derive a formal charge,

Step 1: *Write a correct Lewis structure for the molecule or ion.*

Step 2: *Assign to each atom all its unshared* ***(nonbonding) electrons*** *and one-half its shared* ***(bonding) electrons****.*

Step 3: *Compare the number arrived at in Step 2 with the number of valence electrons in the neutral, unbonded atom.* If the number of electrons assigned to a bonded atom is less than that assigned to the unbonded atom, then more positive charges are in the nucleus than counterbalancing negative charges, and the atom has a positive formal charge. Conversely, if the number of electrons assigned to a bonded atom is greater than that assigned to the unbonded atom, then the atom has a negative formal charge.

$$\text{Formal charge} = \begin{array}{c}\text{Number of valence}\\ \text{electrons in neutral}\\ \text{unbonded atom}\end{array} - \left(\begin{array}{c}\text{All unshared}\\ \text{electrons}\end{array} + \begin{array}{c}\text{One-half of all}\\ \text{shared electrons}\end{array}\right)$$

Draw Lewis Structures of Molecules and Ions

HOW TO 1.1

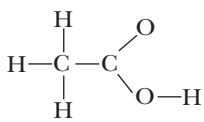
The ability to draw Lewis structures for molecules and ions is a fundamental skill in the study of organic chemistry. The following steps will help you to do this (as you study these steps look at the examples in Table 1.6). As an example, let us draw a Lewis structure of acetic acid, molecular formula $C_2H_4O_2$. Its structural formula, CH_3COOH, gives a hint of the connectivity.

STEP 1: *Determine the number of valence electrons in the molecule or ion.*

To do so, add the number of valence electrons contributed by each atom. For ions, add one electron for each negative charge on the ion, and subtract one electron for each positive charge on the ion. For example, the Lewis structure of the water molecule, H_2O, must show eight valence electrons: one from each hydrogen and six from oxygen. The Lewis structure for the hydroxide ion, OH^-, must also show eight valence electrons: one from hydrogen, six from oxygen, plus one for the negative charge on the ion. For acetic acid the molecular formula is $C_2H_4O_2$. The Lewis structure must show 8(2 carbons) + 4(4 hydrogens) + 12(2 oxygens) = 24 valence electrons.

STEP 2: *Determine the arrangement of atoms in the molecule or ion.*

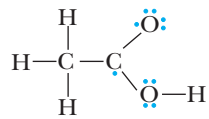
This step is the most difficult part of drawing a Lewis structure. Fortunately, the structural formula of a compound can provide valuable information about connectivity. The order in which the atoms are listed in a structural formula is a guide. For example, the CH_3 part of the structural formula of acetic acid tells you that three hydrogen atoms are bonded to the carbon written on the left, and the COOH part tells you that both oxygens are bonded to the same carbon and a hydrogen is bonded to one of the oxygens.



Except for the simplest molecules and ions, the connectivity must be determined experimentally. For some molecules and ions we give as examples, we ask you to propose a connectivity of the atoms. For most, however, we give you the experimentally determined arrangement.

STEP 3: *Arrange the remaining electrons in pairs so that each atom in the molecule or ion has a complete outer shell. Show a pair of* **bonding electrons** *as a single line between the bonded atoms; show a pair of* **nonbonding electrons** *as a pair of Lewis dots.*

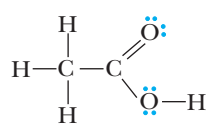
To accomplish this, connect the atoms with single bonds. Then arrange the remaining electrons in pairs so that each atom in the molecule or ion has a complete outer shell. Each hydrogen atom must be surrounded by two electrons. Each atom of carbon, oxygen, and nitrogen, as well as each halogen, must be surrounded by eight electrons (per the octet rule). Recall that each neutral carbon atom has four valence electrons and each neutral oxygen atom has six valence electrons. The structure here shows the required 24 valence electrons. The left carbon has four single bonds and a complete valence shell. Each hydrogen also has a complete valence shell. The lower oxygen has two single bonds and two unshared pairs of electrons and, therefore, has a complete valence shell. The original six valence electrons of the upper oxygen are accounted for, but it does not yet have a filled valence shell. Similarly, the original four valence electrons of the right carbon atom are accounted for but it still does not have a complete valence shell.



Notice that in the structure so far, we have accounted for all valence electrons, but two atoms do not yet have completed valence shells. Furthermore, one carbon atom and one oxygen atom each have a single unpaired electron.

STEP 4: *Use multiple bonds where necessary to eliminate unpaired electrons.*

In a **single bond**, two atoms share one pair of electrons. It is sometimes necessary for atoms to share more than one pair of electrons. In a **double bond**, they share two pairs of electrons; we show a double bond by drawing two parallel lines between the bonded atoms. In a **triple bond**, two atoms share three pairs of electrons; we show a triple bond by three parallel lines between the bonded atoms. The following structure combines the unpaired electrons on carbon and oxygen and creates a double bond (C═O) between these two atoms. The Lewis structure is now complete.



EXAMPLE 1.6

Draw Lewis structures, showing all valence electrons, for these molecules:

(a) H_2O_2 **(b)** CH_3OH **(c)** CH_3Cl

STRATEGY

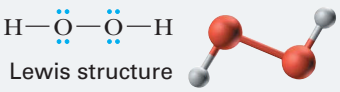
Determine the number of valence electrons and the connectivity of the atoms in each molecule. Connect the bonded atoms by single bonds and then arrange the remaining valence electrons so that each atom has a filled valence shell.

SOLUTION

(a) A Lewis structure for hydrogen peroxide, H_2O_2, must show 6 valence electrons from each oxygen and 1 from each hydrogen, for a total of 12 + 2 = 14 valence electrons. We know that hydrogen forms only one covalent bond, so the connectivity of the atoms must be as follows:

H—O—O—H

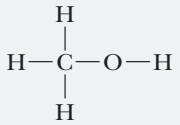
The three single bonds account for 6 valence electrons. We place the remaining 8 valence electrons on the oxygen atoms to give each a complete octet:



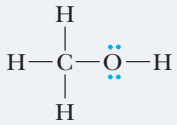
Lewis structure

Ball-and-stick models show only nuclei and covalent bonds; they do not show unshared pairs of electrons

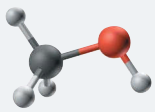
(b) A Lewis structure for methanol, CH_3OH, must show 4 valence electrons from carbon, 1 from each hydrogen, and 6 from oxygen, for a total of 4 + 4 + 6 = 14 valence electrons. The connectivity of the atoms in methanol is given on the left. The five single bonds in this partial structure account for 10 valence electrons. We place the remaining 4 valence electrons on oxygen as two Lewis dot pairs to give it a complete octet.



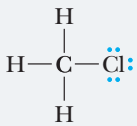
The order of attachment of atoms



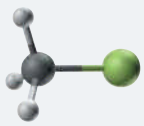
Lewis structure



(c) A Lewis structure for chloromethane, CH_3Cl, must show 4 valence electrons from carbon, 1 from each hydrogen, and 7 from chlorine, for a total of 4 + 3 + 7 = 14. Carbon has four bonds, one to each of the hydrogens and one to chlorine. We place the remaining 6 valence electrons on chlorine as three Lewis dot pairs to complete its octet.



Lewis structure



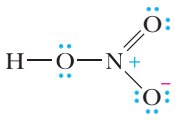
See problems 1.27, 1.28

PROBLEM 1.6

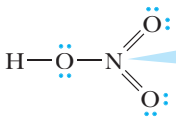
Draw Lewis structures, showing all valence electrons, for these molecules:

(a) C_2H_6 **(b)** CS_2 **(c)** HCN **(d)** HCHO

In writing Lewis structures for molecules and ions, you must remember that elements of the second period, including carbon, nitrogen, and oxygen, can accommodate no more than eight electrons in the four orbitals ($2s$, $2p_x$, $2p_y$, and $2p_z$) of their valence shells. Following are two Lewis structures for nitric acid, HNO_3, each with the correct number of valence electrons, namely, 24; one structure is acceptable and the other is not:



An acceptable Lewis structure



Not an acceptable Lewis structure

The structure on the left is an acceptable Lewis structure. It shows the required 24 valence electrons, and each oxygen and nitrogen has a completed valence shell of 8 electrons. Further, the structure on the left shows a positive formal charge on nitrogen and a negative formal charge on one of the oxygens. An acceptable Lewis structure must show these formal charges. The structure on the right is *not* an acceptable Lewis structure. Although it shows the correct number of valence electrons, it places 10 electrons in the valence shell of

EXAMPLE 1.7

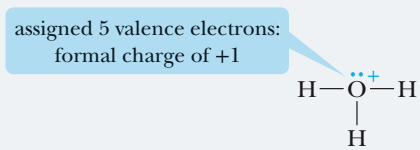
Draw Lewis structures for these ions, and show which atom in each bears the formal charge:
(a) H_3O^+ **(b)** CH_3O^-

STRATEGY

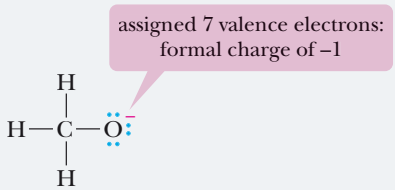
Draw a correct Lewis structure molecule showing all valence electrons on each atom. Then determine the location of the formal charge.

SOLUTION

(a) The Lewis structure for the hydronium ion must show 8 valence electrons: 3 from the three hydrogens, 6 from oxygen, minus 1 for the single positive charge. A neutral, unbonded oxygen atom has 6 valence electrons. To the oxygen atom in H_3O^+, we assign two unshared electrons and one from each shared pair of electrons, giving it a formal charge of 6 – (2 + 3) = +1.



(b) The Lewis structure for the methoxide ion, CH_3O^-, must show 14 valence electrons: 4 from carbon, 6 from oxygen, 3 from the hydrogens, plus 1 for the single negative charge. To carbon, we assign 1 electron from each shared pair, giving it a formal charge of 4 – 4 = 0. To oxygen, we assign 7 valence electrons, giving it a formal charge of 6 – 7 = –1.



See problems 1.30–1.32, 1.34

PROBLEM 1.7

Draw Lewis structures for these ions, and show which atom in each bears the formal charge(s):
(a) $CH_3NH_3^+$ **(b)** CH_3^+

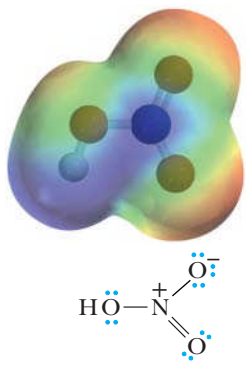
nitrogen, yet the four orbitals of the second shell (2*s*, 2p_x, 2p_y, and 2p_z) can hold no more than 8 valence electrons!

1.3 How Do We Predict Bond Angles and the Shapes of Molecules?

In Section 1.2, we used a shared pair of electrons as the fundamental unit of a covalent bond and drew Lewis structures for several small molecules containing various combinations of single, double, and triple bonds. (See, for example, Table 1.6.) We can predict bond angles in these and other molecules in a very straightforward way by using the concept of **valence-shell electron-pair repulsion (VSEPR)**. According to this concept, the valence electrons of an atom may be involved in the formation of single, double, or triple bonds, or they may be unshared. Each combination creates a region of electron density that, because it is occupied by electrons, is negatively charged. Because like charges repel each other, the various regions of electron density around an atom spread so that each is as far away from the others as possible.

Recall from your prior studies in chemistry that VSEPR can be used to predict the shapes of molecules. This can be demonstrated in a very simple way by using balloons as shown in Figure 1.5.

We can use the example of the balloons to model the shapes that methane (CH_4), ammonia (NH_3), and water (H_2O) assume. As you look at each of these molecules in Figures 1.6–1.8, take note of (1) the number of regions of electron density shown by the Lewis structure, (2) the geometry that is required to maximize the separation of these regions of electron density, and (3) the names of the shapes that result from this treatment using VSEPR.



The Lewis structure of HNO_3 shows the negative formal charge localized on one of the oxygen atoms. The electron density model, on the other hand, shows that the negative charge is distributed equally over the two oxygen atoms on the right. The concept of resonance can explain this phenomenon and will be discussed in Section 1.6. Notice also the intense blue color on nitrogen, which is due to its positive formal charge.

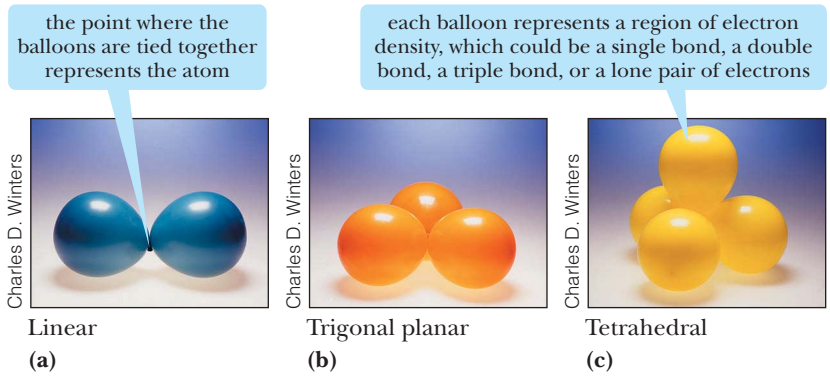


FIGURE 1.5 Balloon models used to predict bond angles. (a) Two balloons assume a linear shape with a bond angle of 180° about the tie point. (b) Three balloons assume a trigonal planar shape with bond angles of 120° about the tie point. (c) Four balloons assume a tetrahedral shape with bond angles of 109.5° about the tie point.

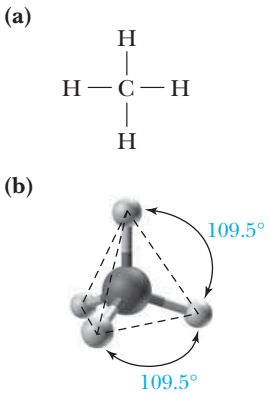


FIGURE 1.6 The shape of a methane molecule, CH_4. (a) Lewis structure and (b) ball-and-stick model. The single bonds occupy four regions of electron density, causing the molecule to be **tetrahedral**. The hydrogens occupy the four corners of a regular tetrahedron, and all H—C—H bond angles are 109.5°.

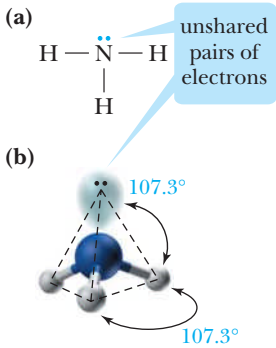


FIGURE 1.7 The shape of an ammonia molecule, NH_3. (a) Lewis structure and (b) ball-and-stick model. The three single bonds and one lone pair of electrons create four regions of electron density. This allows the lone pair and the three hydrogens to occupy the four corners of a tetrahedron. However, we do not take lone pairs of electrons into account when describing the shape of the molecule. For this reason, we describe the geometry of an ammonia molecule as **pyramidal**; that is, the molecule has a shape like a triangular-based pyramid with the three hydrogens at the base and nitrogen at the apex. The observed bond angles are 107.3°. We account for this small difference between the predicted and observed angles by proposing that the unshared pair of electrons on nitrogen repels adjacent electron pairs more strongly than bonding pairs repel each other.

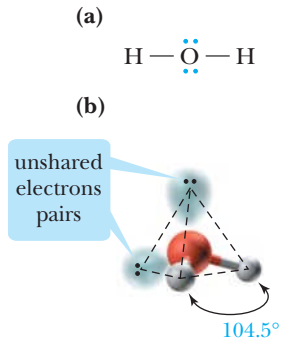


FIGURE 1.8 The shape of a water molecule, H_2O. (a) A Lewis structure and (b) a ball-and-stick model. Using VSEPR, we predict that the four regions of electron density around oxygen are arranged in a tetrahedral manner and that the H—O—H bond angle is 109.5°. Experimental measurements show that the actual H—O—H bond angle is 104.5°, a value smaller than that predicted. We explain this difference between the predicted and observed bond angle by proposing, as we did for NH_3, that unshared pairs of electrons repel adjacent pairs more strongly than do bonding pairs. Note that the distortion from 109.5° is greater in H_2O, which has two unshared pairs of electrons, than it is in NH_3, which has only one unshared pair. We describe the shape of water as **bent**.

A general prediction emerges from this discussion of the shapes of CH_4, NH_3, and H_2O molecules. If a Lewis structure shows four regions of electron density around an atom, then VSEPR predicts a tetrahedral distribution of electron density and bond angles of approximately 109.5°.

In many of the molecules we encounter, an atom is surrounded by three regions of electron density. Figure 1.9 shows Lewis structures for formaldehyde (CH_2O) and ethylene (C_2H_4). As you look at these two molecules, take note of (1) the number of regions of electron density shown by the Lewis structure, (2) the geometry that is required to maximize the separation of these regions of electron density, and (3) the names of the shapes that result from this treatment using VSEPR. Also notice that using VSEPR, we treat a double bond as a single region of electron density.

In still other types of molecules, a central atom is surrounded by only two regions of electron density. Figure 1.10 shows Lewis structures and ball-and-stick models of carbon dioxide (CO_2) and acetylene (C_2H_2). As with double bonds, VSEPR treats triple bonds as one region of electron density.

Table 1.7 summarizes the predictions of VSEPR.

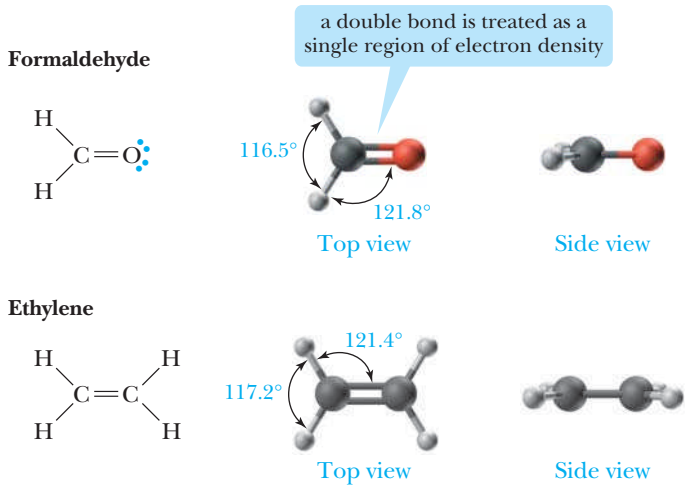


FIGURE 1.9 Shapes of formaldehyde (CH_2O) and ethylene (C_2H_4). In each molecule, the carbons are surrounded by three regions of electron density. Three regions of electron density about an atom are farthest apart when they lie in a plane and make angles of approximately 120° with each other. We describe the geometry about each carbon atom as **trigonal planar**.

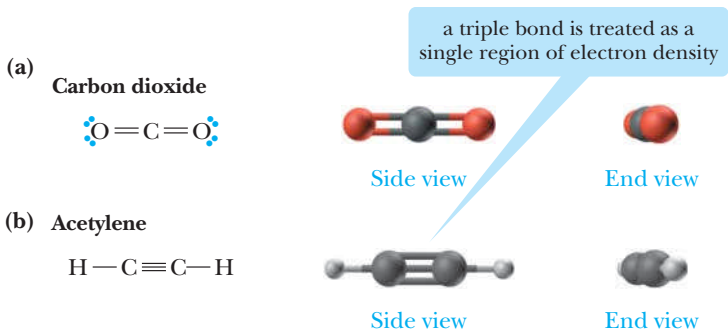


FIGURE 1.10 Shapes of (a) carbon dioxide (CO_2) and (b) acetylene (C_2H_2). In each case, the two regions of electron density are farthest apart if they form a straight line through the central atom and create an angle of 180°. Both carbon dioxide and acetylene are referred to as **linear** molecules.

TABLE 1.7 Predicted Molecular Shapes (VSEPR)

Regions of Electron Density around Central Atom	Predicted Distribution of Electron Density about the Central Atom	Predicted Bond Angles	Examples (Shape of the Molecule)
4	Tetrahedral	109.5°	a solid wedge-shaped bond represents a bond extending out of the plane of the page; a dashed wedge-shaped bond represents a bond extending behind the plane of the page; Methane (tetrahedral); Ammonia (pyramidal); Water (bent)
3	Trigonal planar	120°	Ethylene (planar); Formaldehyde (planar)
2	Linear	180°	Carbon dioxide (linear); Acetylene (linear)

EXAMPLE 1.8

Predict all bond angles in these molecules:

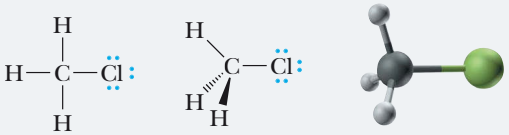
(a) CH_3Cl **(b)** $CH_2{=}CHCl$

STRATEGY

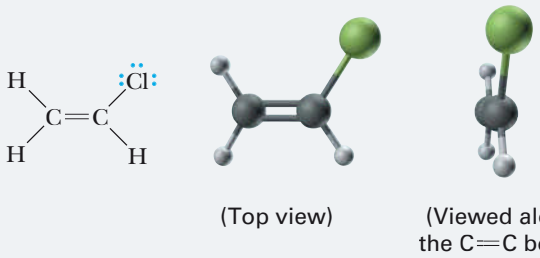
To predict bond angles, first draw a correct Lewis structure for the molecule. Be certain to show all unpaired electrons. Then determine the number of regions of electron density (either 2, 3, or 4) around each atom and use that number to predict bond angles (either 180°, 120°, or 109.5°).

SOLUTION

(a) The Lewis structure for CH_3Cl shows carbon surrounded by four regions of electron density. Therefore, we predict that the distribution of electron pairs about carbon is tetrahedral, that all bond angles are 109.5°, and that the shape of CH_3Cl is tetrahedral:



(b) The Lewis structure for $CH_2{=}CHCl$ shows each carbon surrounded by three regions of electron density. Therefore, we predict that all bond angles are 120°.



(Top view) (Viewed along the C=C bond)

See problems 1.41–1.43

PROBLEM 1.8

Predict all bond angles for these molecules:

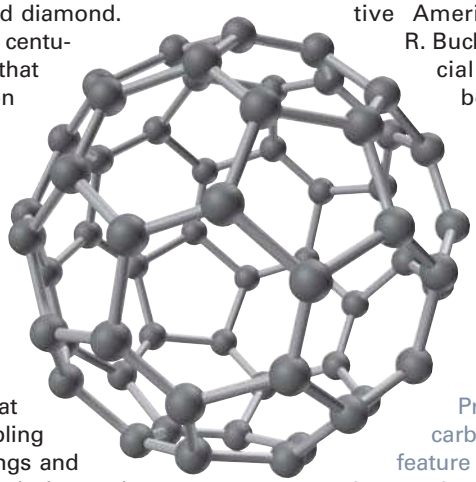
(a) CH_3OH **(b)** CH_2Cl_2 **(c)** H_2CO_3 (carbonic acid)

Chemical Connections 1A

BUCKYBALL: A NEW FORM OF CARBON

Many elements in the pure state can exist in different forms. We are all familiar with the fact that pure carbon is found in two forms: graphite and diamond. These forms have been known for centuries, and it was generally believed that they were the only forms of carbon having extended networks of C atoms in well-defined structures.

But that is not so! The scientific world was startled in 1985 when Richard Smalley of Rice University and Harry W. Kroto of the University of Sussex, England, and their coworkers announced that they had detected a new form of carbon with a molecular formula C_{60}. They suggested that the molecule has a structure resembling a soccer ball: 12 five-membered rings and 20 six-membered rings arranged such that each five-membered ring is surrounded by six-membered rings. This structure reminded its discoverers of a geodesic dome, a structure invented by the innovative American engineer and philosopher R. Buckminster Fuller. Therefore, the official name of the new allotrope of carbon has become fullerene. Kroto, Smalley, and Robert F. Curl were awarded the Nobel Prize for Chemistry in 1996 for their work with fullerenes. Many higher fullerenes, such as C_{70} and C_{84}, have also been isolated and studied.



Question

Predict the bond angles about the carbon atoms in C_{60}. What geometric feature distinguishes the bond angles about each carbon in C_{60} from the bond angles of a compound containing typical carbon–carbon bonds?

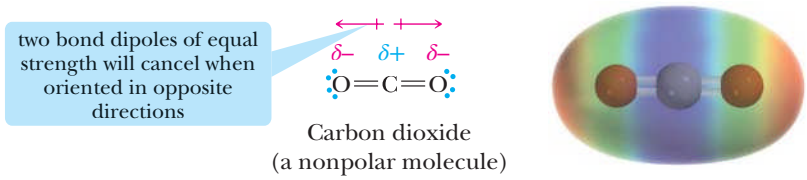
1.4 How Do We Predict If a Molecule Is Polar or Nonpolar?

In Section 1.2C, we used the terms *polar* and *dipole* to describe a covalent bond in which one atom bears a partial positive charge and the other bears a partial negative charge. We also saw that we can use the difference in electronegativity between bonded atoms to determine the polarity of a covalent bond and the direction of its polarity. We can now combine our understanding of bond polarity and molecular geometry (Section 1.3) to predict the polarity of molecules.

A molecule will be nonpolar if (1) it has all nonpolar bonds, or (2) it has polar bonds and the vector sum of its bond dipoles is zero (i.e., the bond dipoles cancel each other). Consider first carbon dioxide, CO_2, a molecule with two polar carbon–oxygen double bonds. Because carbon dioxide is a linear molecule, the vector sum of its two bond dipoles is zero; therefore, this molecule is nonpolar.

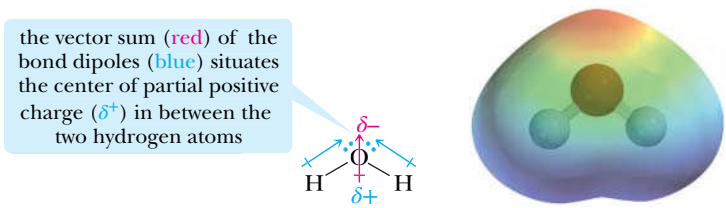
Charles D. Winters/Science Source Images

Carbon dioxide, CO_2, is a nonpolar molecule. Its solid state is often referred to as dry ice.



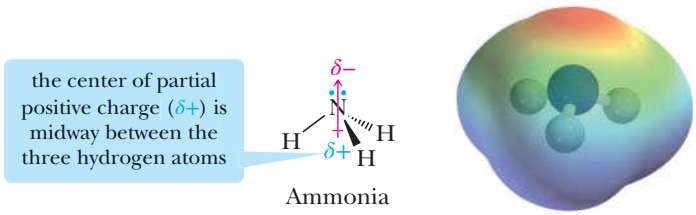
Carbon dioxide
(a nonpolar molecule)

A molecule will be polar if it has polar bonds and the vector sum of its bond dipoles is non-zero. In a water molecule, each O—H bond is polar, with oxygen, the more electronegative atom, bearing a partial negative charge and each hydrogen bearing a partial positive charge. Because water is a bent molecule, the center of its partial positive charge is between the two hydrogen atoms, and the center of its partial negative charge is on oxygen. Thus, water has polar bonds and, because of its geometry, it is a polar molecule.



Water
(a polar molecule)

Ammonia has three polar N—H bonds, and because of its geometry, the vector sum of their bond dipoles does not equal zero. Thus, ammonia is a polar molecule.



Ammonia
(a polar molecule)

EXAMPLE 1.9

Which of these molecules are polar? For each that is polar, specify the direction of its polarity.

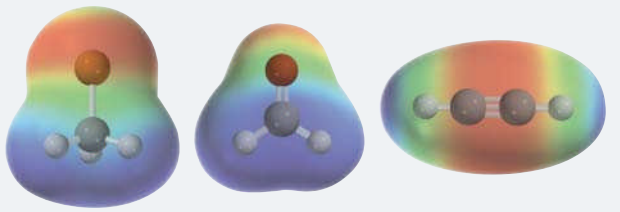
(a) CH_3Cl (b) CH_2O (c) C_2H_2

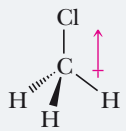
STRATEGY

To determine whether a molecule is polar, first determine if it has polar bonds, and if it does, determine whether the vector sum of the bond dipoles is zero. If the vector sum of the bond dipoles is not zero, the molecule is polar.

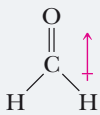
SOLUTION

Both chloromethane (CH_3Cl) and formaldehyde (CH_2O) have polar bonds and, because of their geometry, are polar molecules. Because acetylene (C_2H_2) is linear, and each of its C—H bonds is nonpolar covalent, the molecule is nonpolar.

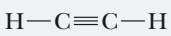




Chloromethane (polar)



Formaldehyde (polar)



Acetylene (nonpolar)

See problems 1.44, 1.46

PROBLEM 1.9

Both carbon dioxide (CO_2) and sulfur dioxide (SO_2) are triatomic molecules. Account for the fact that carbon dioxide is a nonpolar molecule, whereas sulfur dioxide is a polar molecule.

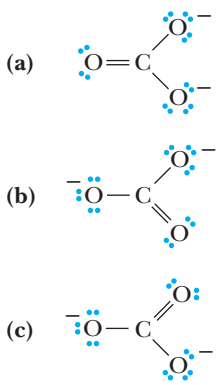


FIGURE 1.11 Three Lewis structures for the carbonate ion.

1.5 What Is Resonance?

As chemists developed a better understanding of covalent bonding in organic compounds, it became obvious that, for a great many molecules and ions, no single Lewis structure provides a truly accurate representation. For example, Figure 1.11 shows three Lewis structures for the carbonate ion, CO_3^{2-}, each of which shows carbon bonded to three oxygen atoms by a combination of one double bond and two single bonds. Each Lewis structure implies that one carbon–oxygen bond is different from the other two. This, however, is not the case; it has been shown that all three carbon–oxygen bonds are identical.

To describe the carbonate ion, as well as other molecules and ions for which no single Lewis structure is adequate, we turn to the theory of resonance.

A. The Theory of Resonance

The theory of resonance was developed by Linus Pauling in the 1930s. According to this theory, many molecules and ions are best described by writing two or more Lewis structures and considering the real molecule or ion to be a composite of these structures. We call

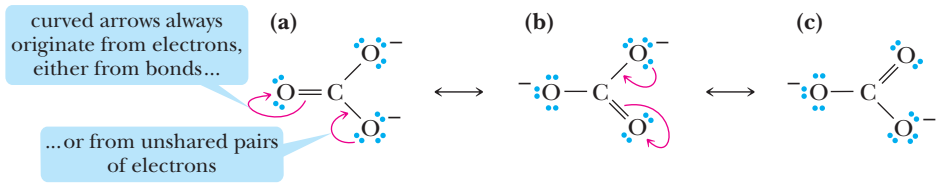


FIGURE 1.12 The carbonate ion represented as a hybrid of three equivalent contributing structures. Curved arrows show the redistribution of valence electrons between one contributing structure and the next.

individual Lewis structures **resonance contributing structures**. We show that the real molecule or ion is a **resonance hybrid** of the various contributing structures by interconnecting them with **double-headed arrows**.

Resonance contributing structures Representations of a molecule or ion that differ only in the distribution of valence electrons.

Resonance hybrid A molecule or ion that is best described as a composite of a number of contributing structures.

Double-headed arrow A symbol used to connect contributing structures.

Figure 1.12 shows three resonance contributing structures for the carbonate ion. The three are equivalent, meaning that they have identical patterns of covalent bonding (each contributing structure has one double bond and two single bonds) and are of equal energy.

Use of the term *resonance* for this theory of covalent bonding might suggest to you that bonds and electron pairs constantly change back and forth from one position to another over time. This notion is not at all correct. The carbonate ion, for example, has one and only one real structure. The problem is ours: How do we draw that one real structure? The resonance method is a way to describe the real structure and at the same time retain Lewis structures with electron-pair bonds. Thus, although we realize that the carbonate ion is not accurately represented by any one contributing structure shown in Figure 1.12, we continue to represent it as one of these for convenience. We understand, of course, that what is intended is the resonance hybrid.

A final note. Do not confuse resonance contributing structures with equilibration among different species. A molecule described as a resonance hybrid is not equilibrating among individual electron configurations. Rather, the molecule has only one structure, which is best described as a hybrid of its various contributing structures. The colors of the color wheel provide a good analogy. Green is not a primary color; the colors yellow and blue are mixed to make green. You can think of molecules represented by resonance hybrids as being green. Green is not sometimes yellow and sometimes blue. Green is green! In an analogous way, a molecule described as a resonance hybrid is not sometimes one contributing structure and sometimes another. It is a single structure all of the time—the resonance hybrid.

B. Curved Arrows and Electron Pushing

Notice in Figure 1.12 that the only change from resonance contributing structure (a) to (b) and then from (b) to (c) is a redistribution of valence electrons. To show how this redistribution of valence electrons occurs, chemists use a symbol called a **curved arrow**, which shows the repositioning of an electron pair from its origin (the tail of the arrow) to its destination (the head of the arrow). The repositioning may be from an atom to an adjacent bond or from a bond to an adjacent atom.

Curved arrow A symbol used to show the redistribution of valence electrons.

A curved arrow is nothing more than a bookkeeping symbol for keeping track of electron pairs or, as some call it, **electron pushing**. Do not be misled by its simplicity. Electron pushing will help you see the relationship between contributing structures. Furthermore, it will help you follow bond-breaking and bond-forming steps in organic reactions. Understanding this type of electron pushing is a survival skill in organic chemistry; your success in this course depends on it.

C. Rules for Writing Acceptable Resonance Contributing Structures

You must follow these four rules in writing acceptable resonance contributing structures:

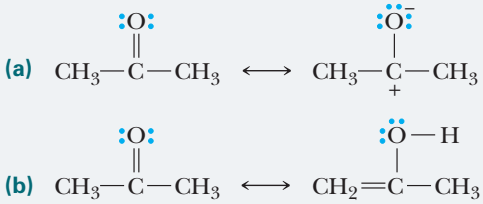
1. All contributing structures must have the same number of valence electrons.
2. All contributing structures must obey the rules of covalent bonding; thus, no contributing structure may have more than 2 electrons in the valence shell of hydrogen or more

than 8 electrons in the valence shell of a second-period element. Third-period elements, such as sulfur and phosphorus, may have up to 12 electrons in their valence shells.

3. The positions of all nuclei must be the same; that is, contributing structures differ only in the distribution of valence electrons.
4. All contributing structures must have the same total number of paired and unpaired electrons.

EXAMPLE 1.10

Which sets are pairs of acceptable resonance contributing structures?



STRATEGY

The concept being examined here is that resonance involves the redistribution of valence electrons; the connectivity of atoms does not change.

SOLUTION

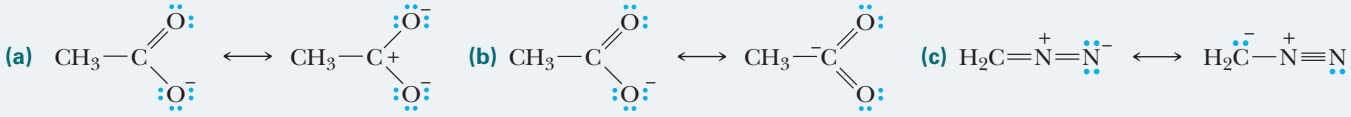
(a) A pair of resonance contributing structures. They differ only in the distribution of valence electrons.

(b) Not a pair of resonance contributing structures. They differ in the arrangement of their atoms. Oxygen is bonded to a hydrogen atom in the Lewis structure on the right, but the other structure contains no such bond.

See problem 1.47

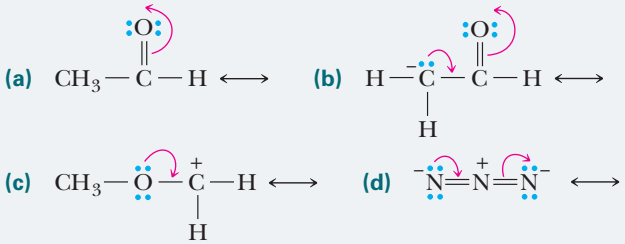
PROBLEM 1.10

Which sets are pairs of resonance contributing structures?



EXAMPLE 1.11

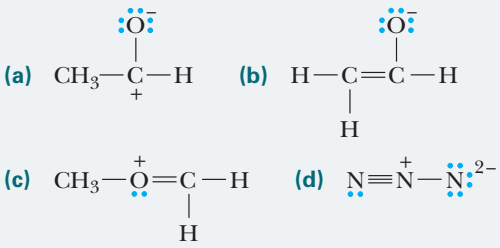
Draw the resonance contributing structure indicated by the curved arrows. Be certain to show all valence electrons and all formal charges.



STRATEGY

Any curved arrow that points to an atom will generate a lone pair of electrons. Any curved arrow that points to a bond will result in an additional bond on top of the original bond. That is, a single bond will become a double bond and a double bond will become a triple bond.

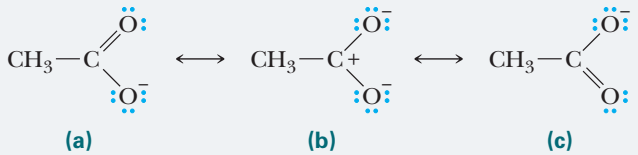
SOLUTION



See problems 1.48, 1.50

PROBLEM 1.11

Use curved arrows to show the redistribution of valence electrons in converting resonance contributing structure (a) to (b) and then (b) to (c). Also show, using curved arrows, how (a) can be converted to (c) without going through (b).



1.6 What Is the Orbital Overlap Model of Covalent Bonding?

As much as the Lewis and VSEPR models help us to understand covalent bonding and the geometry of molecules, they leave many questions unanswered. The most important of these questions is the relation between molecular structure and chemical reactivity. For example, carbon–carbon double bonds are different in chemical reactivity from carbon–carbon single bonds. Most carbon–carbon single bonds are quite unreactive but carbon–carbon double bonds, as we will see in Chapter 5, react with a wide variety of reagents. The Lewis model and VSEPR give us no way to account for these differences. Therefore, let us turn to a newer model of covalent bonding, namely, the formation of covalent bonds by the overlap of atomic orbitals.

A. Shapes of Atomic Orbitals

One way to visualize the electron density associated with a particular orbital is to draw a boundary surface around the region of space that encompasses some arbitrary percentage of the charge density associated with that orbital. Most commonly, we draw the boundary surface at 95%. Drawn in this manner, all *s* orbitals have the shape of a sphere with its center at the nucleus (Figure 1.13). Of the various *s* orbitals, the sphere representing the 1*s* orbital is the smallest. A 2*s* orbital is a larger sphere, and a 3*s* orbital is an even larger sphere.

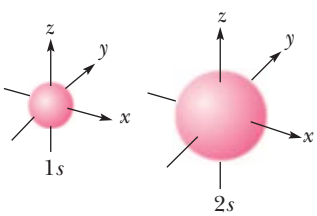


FIGURE 1.13 Shapes of 1*s* and 2*s* atomic orbitals.

Figure 1.14 shows the three-dimensional shapes of the three 2*p* orbitals, combined in one diagram to illustrate their relative orientations in space. Each 2*p* orbital consists of two lobes arranged in a straight line with the nucleus in the middle. The three 2*p* orbitals are mutually perpendicular and are designated $2p_x$, $2p_y$, and $2p_z$.

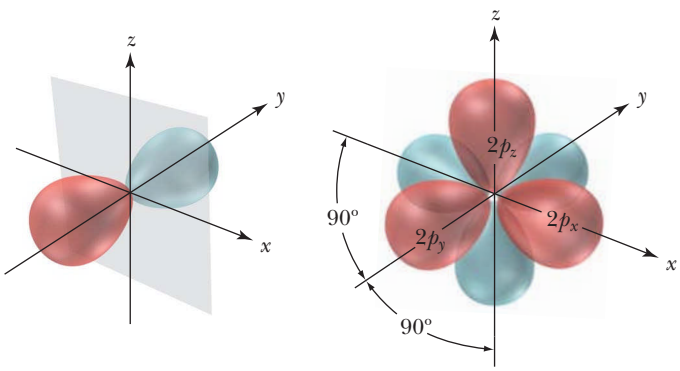


FIGURE 1.14 Shapes of $2p_x$, $2p_y$, and $2p_z$ atomic orbitals. The three 2*p* orbitals are mutually perpendicular. One lobe of each orbital is shown in red, the other in blue.

B. Formation of a Covalent Bond by the Overlap of Atomic Orbitals

Sigma (σ) bond A covalent bond in which the overlap of atomic orbitals is concentrated along the bond axis.

According to the orbital overlap model, a covalent bond is formed when a portion of an atomic orbital of one atom overlaps a portion of an atomic orbital of another atom. In forming the covalent bond in H_2, for example, two hydrogens approach each other so that their 1*s* atomic orbitals overlap to form a sigma covalent bond (Figure 1.15). A **sigma (σ) bond** is a covalent bond in which orbitals overlap along the axis joining the two nuclei.

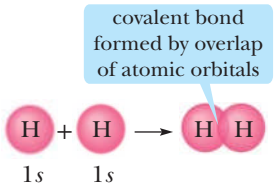
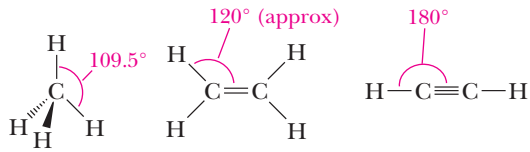


FIGURE 1.15 Formation of the covalent bond in H_2 by the overlap of the 1*s* atomic orbitals of each hydrogen.

C. Hybridization of Atomic Orbitals

The formation of a covalent bond between two hydrogen atoms is straightforward. The formation of covalent bonds with second-period elements, however, presents the following problem: In forming covalent bonds, atoms of carbon, nitrogen, and oxygen (all second-period elements) use 2*s* and 2*p* atomic orbitals. The three 2*p* atomic orbitals are at angles of 90° to one another (Figure 1.14), and if atoms of second-period elements used these orbitals to form covalent bonds, the bond angles around each would be approximately 90°. Bond angles of 90°, however, are rarely observed in organic molecules. What we find, instead, are bond angles of approximately 109.5° in molecules with only single bonds, 120° in molecules with double bonds, and 180° in molecules with triple bonds:



Hybrid orbitals An orbital produced from the combination of two or more atomic orbitals.

To account for these observed bond angles, Pauling proposed that atomic orbitals combine to form new orbitals, called **hybrid orbitals**. In your introductory chemistry course, you learned about several types of hybrid orbitals made up from *s*, *p*, and even *d* atomic orbitals. In organic chemistry, because we deal almost exclusively with elements of the first and second periods of the Periodic Table, we are mostly concerned with the hybrid orbitals that result from the combination of *s* and *p* atomic orbitals. These are aptly named the *sp*-type hybrid orbitals, of which there are three types. The type and number of hybrid orbitals formed are equal to the number of atomic orbitals combined. Elements of the second period form these three types of hybrid orbitals, designated sp^3, sp^2, and *sp*, each of which can contain up to two electrons. We review these hybrid orbitals for you here. Keep in mind that superscripts in the designation of hybrid orbitals tell you how many atomic orbitals have been combined to form the hybrid orbitals. The designation sp^3, for example, tells you that *one s* atomic orbital and *three p* atomic orbitals are combined in forming the hybrid orbital. Do not confuse this use of superscripts with how we use superscripts in writing a ground-state electron configuration—for example, $1s^2 2s^2 2p^5$ for fluorine. In the case of an electron configuration, superscripts tell you the number of electrons in each orbital or set of orbitals.

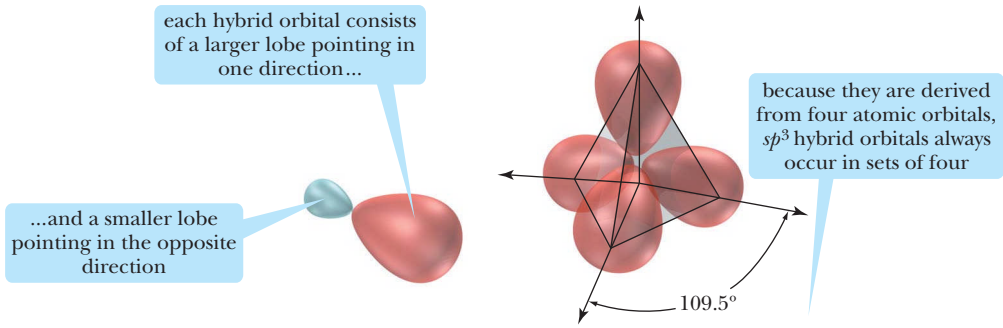
As you review each type of hybrid orbital in the following subsections, take note of (1) the number and types of atomic orbitals that were combined to make the hybrid orbitals, (2) the number of *p* orbitals that remain uncombined, and (3) the three-dimensional arrangement in space of the hybrid orbitals and any uncombined *p* orbitals. In particular, you will find that these three-dimensional arrangements will retain the names (tetrahedral, trigonal planar, linear) and bond angles (109.5°, 120°, and 180°) used to describe the shapes of molecules in our section on VSEPR (Section 1.3).

D. sp^3 Hybrid Orbitals: Bond Angles of Approximately 109.5°

sp^3 Hybrid orbital An orbital produced by the combination of one *s* atomic orbital and three *p* atomic orbitals.

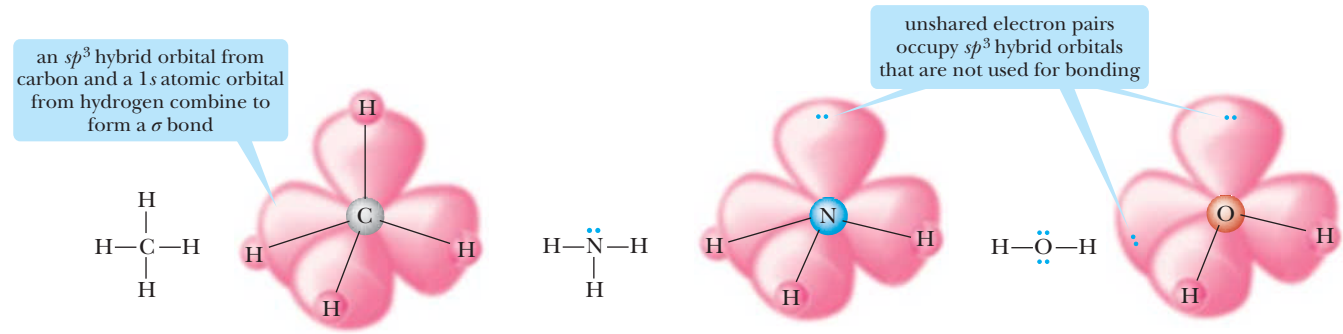
The combination of one 2*s* atomic orbital and three 2*p* atomic orbitals forms four equivalent **sp^3 hybrid orbitals** (Figure 1.16).

In Section 1.2, we described the covalent bonding in CH_4, NH_3, and H_2O in terms of the Lewis model, and in Section 1.3 we used VSEPR to predict bond angles of approximately 109.5° in each molecule. Figure 1.17 shows the bonding in these molecules in terms of the overlap of orbitals. Notice that the central atom in each compound uses four sp^3



(a) An sp^3 orbital **(b)** Four tetrahedral sp^3 orbitals

FIGURE 1.16 sp^3 Hybrid orbitals. (a) Representation of a single sp^3 hybrid orbital showing two lobes of unequal size. (b) Three-dimensional representation of four sp^3 hybrid orbitals, which point toward the corners of a regular tetrahedron. The smaller lobes of each sp^3 hybrid orbital are hidden behind the larger lobes.



	Methane	**Ammonia**	**Water**
Arrangement of orbitals:	Tetrahedral	Tetrahedral	Tetrahedral
Shape of molecule:	Tetrahedral	Pyramidal	Bent

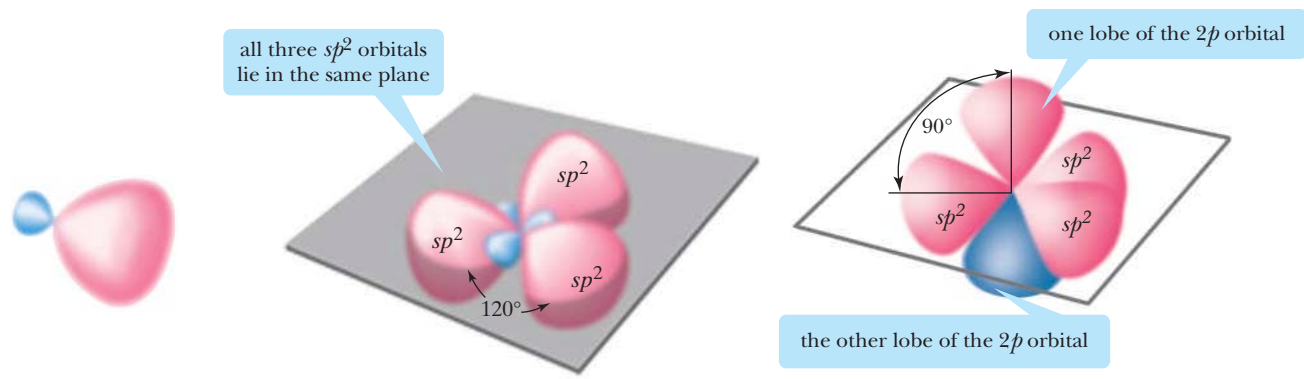
FIGURE 1.17 Orbital overlap models of methane, ammonia, and water.

hybrid orbitals to either form a sigma (σ) bond with a hydrogen atom or to hold unshared pairs of electrons. In each case, the orbitals are arranged tetrahedrally, while the shape that describes each molecule is based only on the arrangement of atoms.

E. sp^2 Hybrid Orbitals: Bond Angles of Approximately 120°

The combination of one 2s atomic orbital and two 2p atomic orbitals forms three equivalent ***sp*² hybrid orbitals** (Figure 1.18). Because they are derived from three atomic orbitals, sp^2 hybrid orbitals always occur in sets of three. The third 2p atomic orbital (remember $2p_x$, $2p_y$, and $2p_z$) is not involved in hybridization and consists of two lobes lying perpendicular to the plane of the hybrid orbitals [Figure 1.18(c)].

***sp*² Hybrid orbital** An orbital produced by the combination of one *s* atomic orbital and two *p* atomic orbitals.



(a) An sp^2 orbital **(b)** Three sp^2 orbitals **(c)**

FIGURE 1.18 sp^2 Hybrid orbitals. (a) A single sp^2 hybrid orbital showing two lobes of unequal size. (b) The three sp^2 hybrid orbitals with their axes in a plane at angles of 120°. (c) The unhybridized 2p atomic orbital perpendicular to the plane created by the three sp^2 hybrid orbitals.

Second-period elements use sp^2 hybrid orbitals to form double bonds. Figure 1.19(a) shows a Lewis structure for ethylene, C_2H_4. A sigma bond between the carbons in ethylene forms by the overlap of sp^2 hybrid orbitals along a common axis [Figure 1.19(b)]. Each carbon also forms sigma bonds to two hydrogens. The remaining $2p$ orbitals on adjacent carbon atoms lie parallel to each other and overlap to form a pi bond [Figure 1.19(c)]. A **pi (π) bond** is a covalent bond formed by the overlap of parallel p orbitals. Because of the lesser degree of overlap of orbitals forming pi bonds compared with those forming sigma bonds, pi bonds are generally weaker than sigma bonds.

Pi (π) bond A covalent bond formed by the overlap of parallel *p* orbitals.

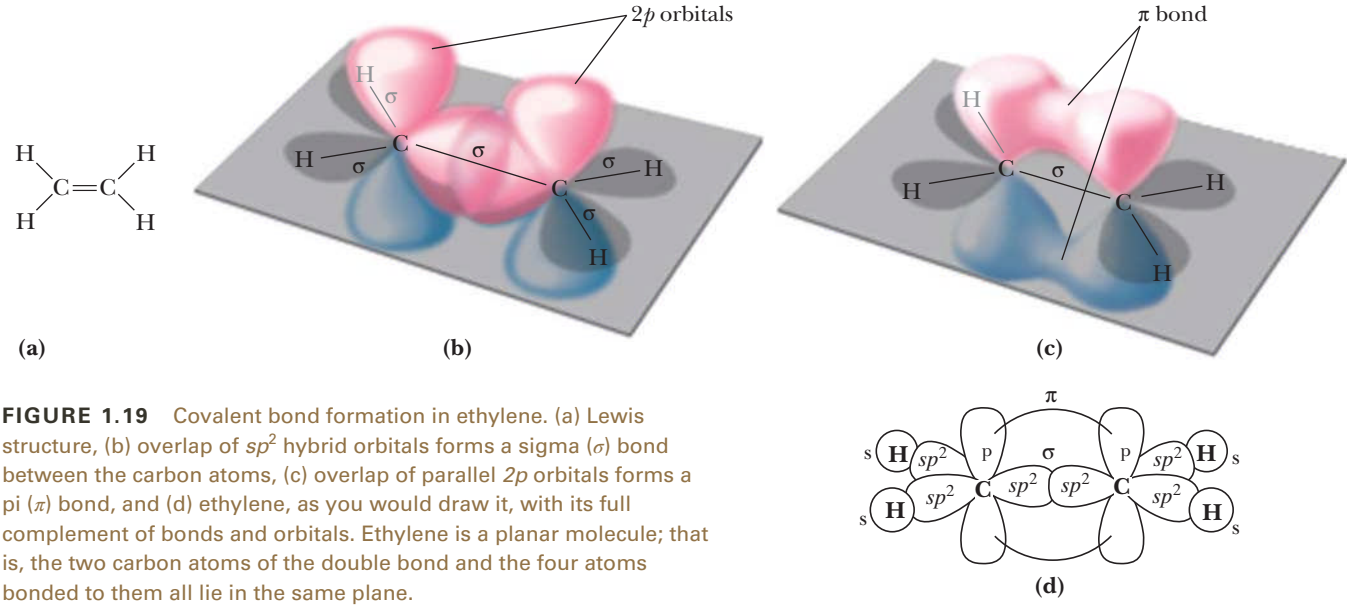


FIGURE 1.19 Covalent bond formation in ethylene. (a) Lewis structure, (b) overlap of sp^2 hybrid orbitals forms a sigma (σ) bond between the carbon atoms, (c) overlap of parallel *2p* orbitals forms a pi (π) bond, and (d) ethylene, as you would draw it, with its full complement of bonds and orbitals. Ethylene is a planar molecule; that is, the two carbon atoms of the double bond and the four atoms bonded to them all lie in the same plane.

The orbital overlap model describes all double bonds in the same way that we have described a carbon–carbon double bond. In formaldehyde, CH_2O, the simplest organic molecule containing a carbon–oxygen double bond, carbon forms sigma bonds to two hydrogens by the overlap of an sp^2 hybrid orbital of carbon and the $1s$ atomic orbital of each hydrogen. Carbon and oxygen are joined by a sigma bond formed by the overlap of sp^2 hybrid orbitals and a pi bond formed by the overlap of unhybridized $2p$ atomic orbitals (Figure 1.20).

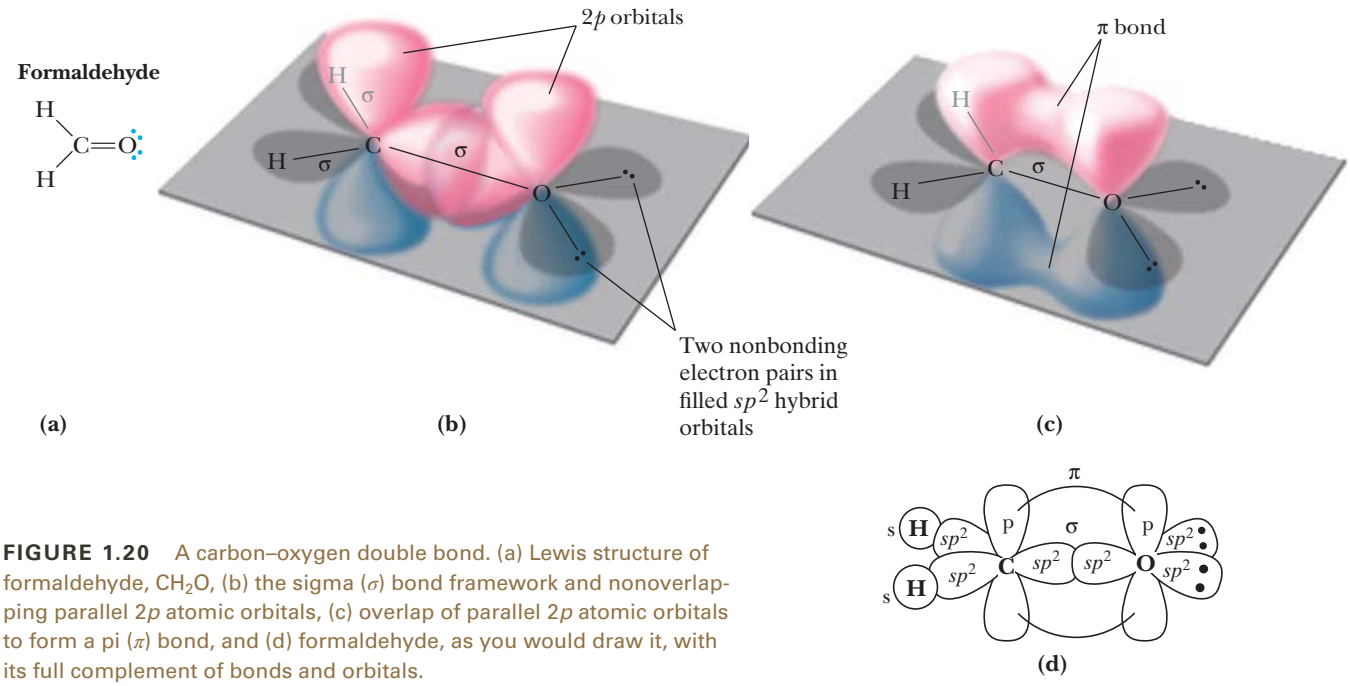


FIGURE 1.20 A carbon–oxygen double bond. (a) Lewis structure of formaldehyde, CH_2O, (b) the sigma (σ) bond framework and nonoverlapping parallel $2p$ atomic orbitals, (c) overlap of parallel $2p$ atomic orbitals to form a pi (π) bond, and (d) formaldehyde, as you would draw it, with its full complement of bonds and orbitals.

F. *sp* Hybrid Orbitals: Bond Angles of Approximately 180°

The combination of one 2*s* atomic orbital and one 2*p* atomic orbital forms two equivalent ***sp* hybrid orbitals**. Because they are derived from two atomic orbitals, *sp* hybrid orbitals always occur in sets of two (Figure 1.21).

Figure 1.22 shows a Lewis structure and an orbital overlap diagram for acetylene, C_2H_2. A carbon–carbon triple bond consists of one sigma bond and two pi bonds. The sigma bond is formed by the overlap of *sp* hybrid orbitals. One pi bond is formed by the overlap of a pair of parallel 2*p* atomic orbitals. The second pi bond is formed by the overlap of a second pair of parallel 2*p* atomic orbitals.

***sp* Hybrid orbitals** A hybrid atomic orbital produced by the combination of one *s* atomic orbital and one *p* atomic orbital.

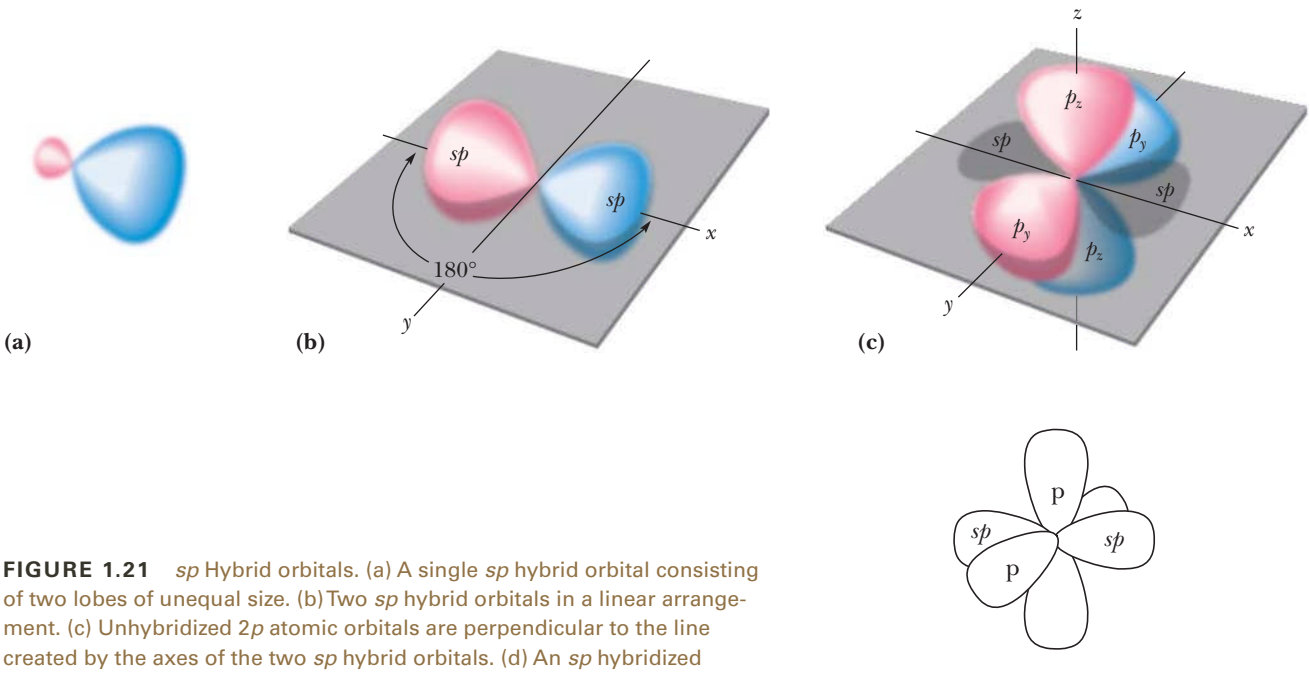


FIGURE 1.21 *sp* Hybrid orbitals. (a) A single *sp* hybrid orbital consisting of two lobes of unequal size. (b) Two *sp* hybrid orbitals in a linear arrangement. (c) Unhybridized 2*p* atomic orbitals are perpendicular to the line created by the axes of the two *sp* hybrid orbitals. (d) An *sp* hybridized atom, as you would draw it, with its full complement of orbitals.

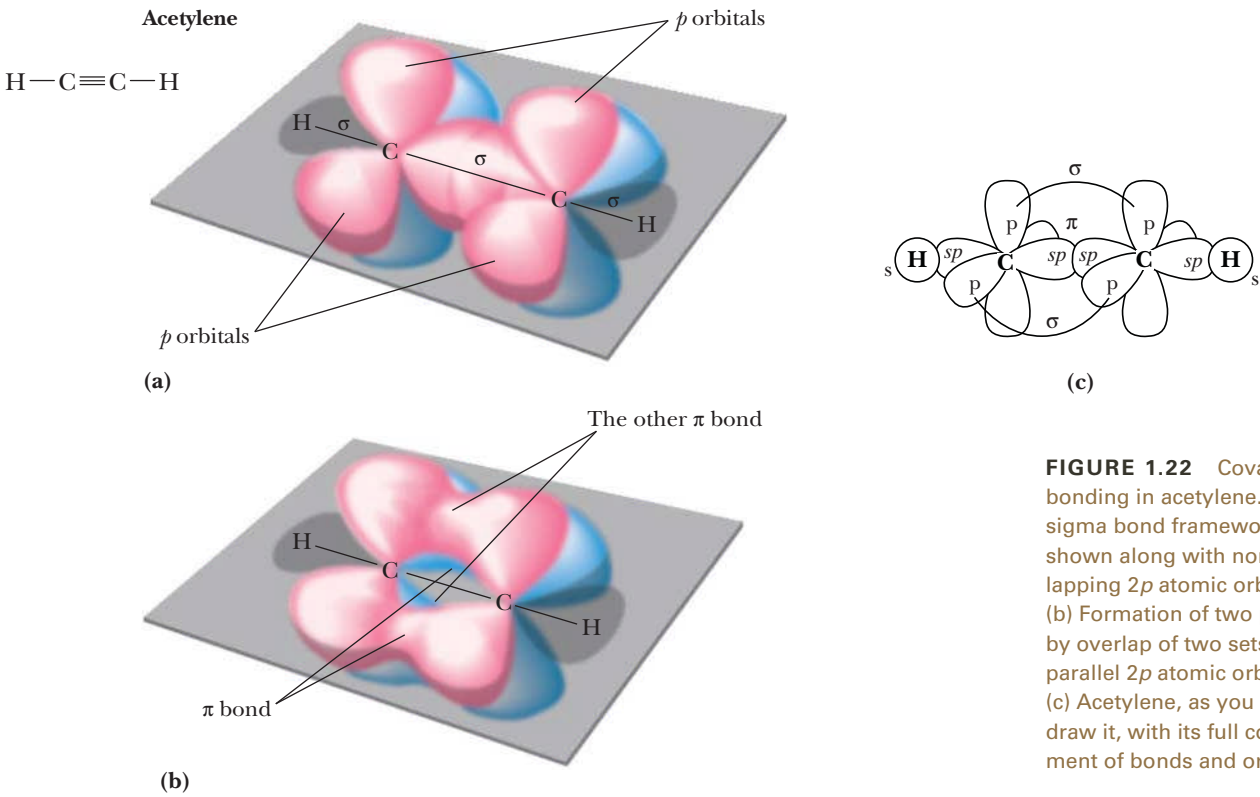
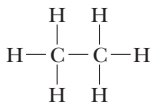
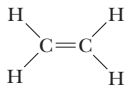


FIGURE 1.22 Covalent bonding in acetylene. (a) The sigma bond framework shown along with nonoverlapping 2*p* atomic orbitals. (b) Formation of two pi bonds by overlap of two sets of parallel 2*p* atomic orbitals. (c) Acetylene, as you would draw it, with its full complement of bonds and orbitals.

Table 1.8 summarizes the relationship among the number of groups bonded to carbon, orbital hybridization, and the types of bonds involved.

TABLE 1.8 Covalent Bonding of Carbon

Groups Bonded to Carbon	Orbital Hybridization	Predicted Bond Angles	Types of Bonds to Carbon	Example	Name
4	sp^3	109.5°	four sigma bonds		ethane
3	sp^2	120°	three sigma bonds and one pi bond		ethylene
2	sp	180°	two sigma bonds and two pi bonds		acetylene

EXAMPLE 1.12

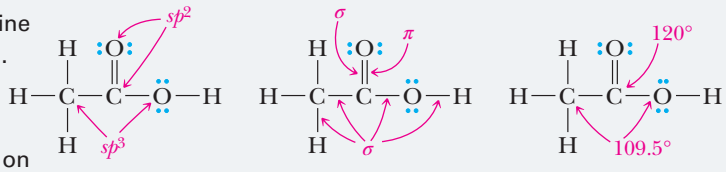
Describe the bonding in acetic acid, CH_3COOH, in terms of the orbitals involved, and predict all bond angles.

STRATEGY

First draw a Lewis structure for acetic acid and then determine the number of regions of electron density about each atom.

SOLUTION

The following are three identical Lewis structures. Labels on the first structure point to atoms and show hybridization. Labels on the second structure point to bonds and show the type of bond, either sigma or pi. Labels on the third structure point to atoms and show bond angles about each atom as predicted by valence-shell electron-pair repulsion.



See problems 1.51, 1.52

PROBLEM 1.12

Describe the bonding in these molecules in terms of the atomic orbitals involved, and predict all bond angles:

(a) $CH_3CH{=}CH_2$
(b) CH_3NH_2

1.7 What Are Functional Groups?

Over 10 million organic compounds have been discovered or made by organic chemists! Surely it would seem to be an almost impossible task to learn the physical and chemical properties of this many compounds. Fortunately, the study of organic compounds is not as formidable a task as you might think. While organic compounds can undergo a wide variety of chemical reactions, only certain portions of their structure are changed in any particular reaction. The part of an organic molecule that undergoes chemical reactions is called a **functional group**, and, as we will see, the same functional group, in whatever organic molecule we find it, undergoes the same types of chemical reactions. Therefore, you do not have to study the chemical reactions of even a fraction of the 10 million known organic compounds. Instead you need only to identify a few characteristic types of functional groups and then study the chemical reactions that each undergoes.

Functional group An atom or a group of atoms within a molecule that shows a characteristic set of physical and chemical properties.

Functional groups are also important because they are the units by which we divide organic compounds into families of compounds. For example, we group those compounds which contain an —OH (hydroxyl) group bonded to a tetrahedral carbon into a family called alcohols, and compounds containing a —COOH (carboxyl) group into a family called carboxylic acids. In Table 1.9, we introduce seven of the most common functional groups. A complete list of all functional groups we will study is on page I.10 at the end of the text.

TABLE 1.9 Seven Common Functional Groups

Functional Group	Name of Group	Present In	Example	Name of Example
—OH	hydroxyl	alcohols	CH_3CH_2OH	Ethanol
$-NH_2$	amino	amines	$CH_3CH_2NH_2$	Ethanamine
$-\overset{\overset{O}{\|}}{C}-H$	carbonyl	aldehydes	$CH_3\overset{\overset{O}{\|}}{C}H$	Ethanal
$-\overset{\overset{O}{\|}}{C}-$	carbonyl	ketones	$CH_3\overset{\overset{O}{\|}}{C}CH_3$	Acetone
$-\overset{\overset{O}{\|}}{C}-OH$	carboxyl	carboxylic acids	$CH_3\overset{\overset{O}{\|}}{C}OH$	Acetic acid
$-\overset{\overset{O}{\|}}{C}-O-$	carboxylate	esters	$CH_3\overset{\overset{O}{\|}}{C}OCH_3$	Ethyl acetate
$-\overset{\overset{O}{\|}}{C}-\underset{\|}{N}-$	carbamide	amides	$CH_3\overset{\overset{O}{\|}}{C}NH_2$	Acetamide

At this point, our concern is only pattern recognition—that is, how to recognize these seven functional groups when you see them and how to draw structural formulas of molecules containing them.

Finally, functional groups serve as the basis for naming organic compounds. Ideally, each of the 10 million or more organic compounds must have a name that is different from every other compound.

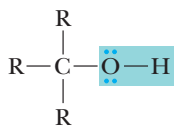
To summarize, functional groups

- are sites of chemical reaction; a particular functional group, in whatever compound we find it, undergoes the same types of chemical reactions.
- determine, in large measure, the physical properties of a compound.
- are the units by which we divide organic compounds into families.
- serve as a basis for naming organic compounds.

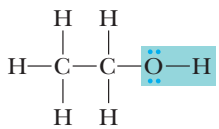
A. Alcohols

Hydroxyl group An —OH group.

The functional group of an **alcohol** is an **—OH (hydroxyl) group** bonded to a tetrahedral (sp^3 hybridized) carbon atom. In the general formula that follows, we use the symbol R to indicate either a hydrogen or another carbon group. The important point in the general structure is that the —OH group is bonded to a tetrahedral carbon atom:



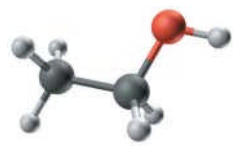
Functional group (R=H or carbon group)



Structural formula

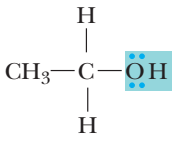
CH_3CH_2OH

Condensed structural formula

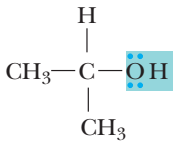


The rightmost representation of this alcohol is a **condensed structural formula**, CH_3CH_2OH. In a condensed structural formula, CH_3 indicates a carbon bonded to three hydrogens, CH_2 indicates a carbon bonded to two hydrogens, and CH indicates a carbon bonded to one hydrogen. We generally do not show unshared pairs of electrons in a condensed structural formula.

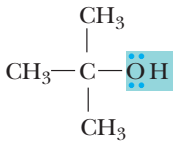
Alcohols are classified as **primary (1°)**, **secondary (2°)**, or **tertiary (3°)**, depending on the number of carbon atoms bonded to the carbon bearing the —OH group:



A 1° alcohol



A 2° alcohol



A 3° alcohol

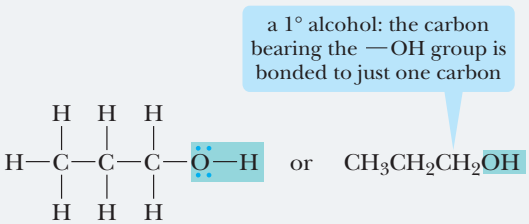
EXAMPLE 1.13

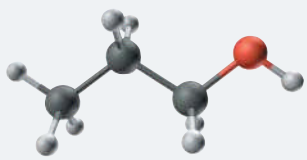
Write condensed structural formulas for the two alcohols with the molecular formula C_3H_8O. Classify each as primary, secondary, or tertiary.

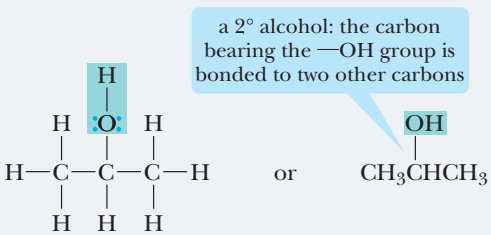
STRATEGY

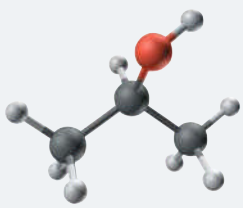
First, bond the three carbon atoms in a chain with the —OH (hydroxyl) group bonded to either an end carbon or the middle carbon of the chain. Then, to complete each structural formula, add seven hydrogens so that each carbon has four bonds to it.

SOLUTION









See problems 1.53–1.56, 1.58, 1.59

PROBLEM 1.13

Write condensed structural formulas for the four alcohols with the molecular formula $C_4H_{10}O$. Classify each as primary, secondary, or tertiary.

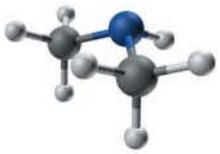
B. Amines

Amino group An sp^3 hybridized nitrogen atom bonded to one, two, or three carbon groups.

The functional group of an amine is an **amino group**—a nitrogen atom bonded to one, two, or three carbon atoms. In a **primary (1°) amine**, nitrogen is bonded to one carbon atom. In a **secondary (2°) amine**, it is bonded to two carbon atoms, and in a **tertiary (3°) amine**, it is bonded to three carbon atoms. The second and third structural formulas that follow can be written in a more abbreviated form by collecting the CH_3 groups and writing them as $(CH_3)_2NH$ and $(CH_3)_3N$, respectively.

$CH_3\ddot{N}H_2$

Methylamine
(a 1° amine)



$CH_3\ddot{N}H$ or $(CH_3)_2\ddot{N}H$
|
CH_3

Dimethylamine
(a 2° amine)

$CH_3\ddot{N}CH_3$ or $(CH_3)_3\ddot{N}$
|
CH_3

Trimethylamine
(a 3° amine)

EXAMPLE 1.14

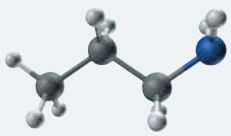
Write condensed structural formulas for the two primary (1°) amines with the molecular formula C_3H_9N.

STRATEGY

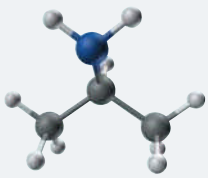
For a primary amine, draw a nitrogen atom bonded to two hydrogens and one carbon. The nitrogen may be bonded to the three-carbon chain in two different ways. Then add the seven hydrogens to give each carbon four bonds and give the correct molecular formula.

SOLUTION

$CH_3CH_2CH_2\ddot{N}H_2$



$CH_3CH(\ddot{N}H_2)CH_3$



See problems 1.53–1.56, 1.58, 1.59

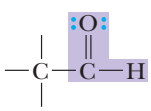
PROBLEM 1.14

Write condensed structural formulas for the three secondary amines with molecular formula $C_4H_{11}N$.

C. Aldehydes and Ketones

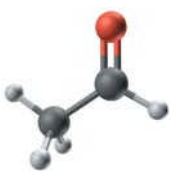
Both aldehydes and ketones contain a **C═O (carbonyl) group**. The **aldehyde** functional group contains a carbonyl group bonded to a hydrogen. In formaldehyde, CH_2O, the simplest aldehyde, the carbonyl carbon is bonded to two hydrogen atoms. In a condensed structural formula, the aldehyde group may be written showing the carbon–oxygen double bond as CH═O, or, alternatively, it may be written —CHO. The functional group of a **ketone** is a carbonyl group bonded to two carbon atoms.

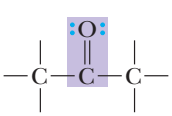
Carbonyl group A C═O group.



Functional group

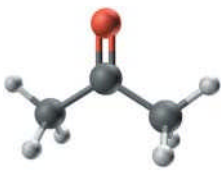
An aldehyde





Functional group

A ketone



EXAMPLE 1.15

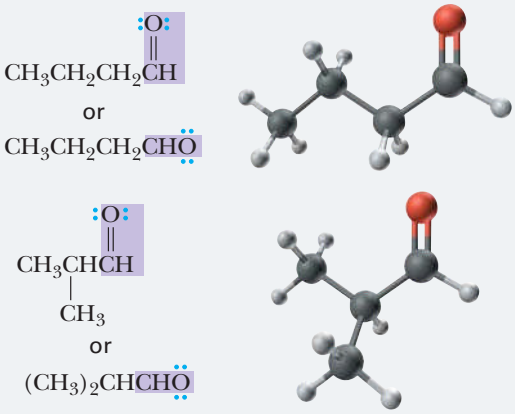
Write condensed structural formulas for the two aldehydes with the molecular formula C_4H_8O.

STRATEGY

First, draw the functional group of an aldehyde and add the remaining carbons, which in this case may be bonded in two different ways. Then, add seven hydrogens to complete the four bonds of each carbon and give the correct molecular formula: Note that the aldehyde group may be written showing the carbon–oxygen double bond as C═O, or, alternatively, it may be written —CHO.

See problems 1.53–1.56, 1.58, 1.59

SOLUTION



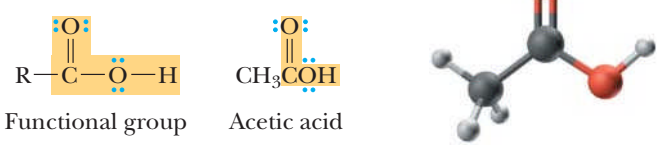
PROBLEM 1.15

Write condensed structural formulas for the three ketones with the molecular formula $C_5H_{10}O$.

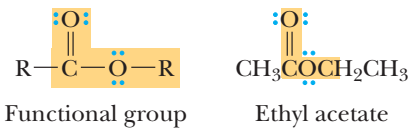
D. Carboxylic Acids, Esters, and Amides

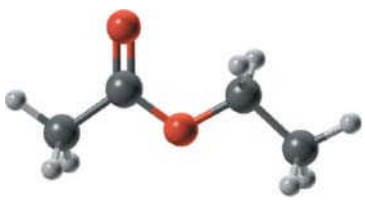
Carboxyl group A —COOH group.

The functional group of a **carboxylic acid** is a **—COOH (carboxyl:** *carb*onyl + hydr*oxyl*) group. In an **ester**, the —OH group is replaced with an —OR group, and in an **amide**, an $—NH_2$, —NHR, or $—NR_2$ group is bonded to the carbonyl group:

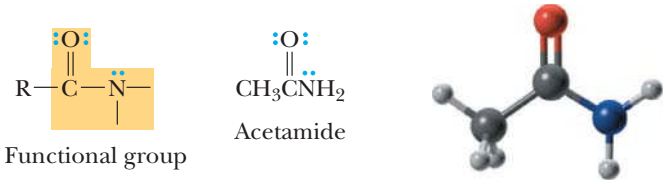


Carboxylic acid





Ester



Amide

EXAMPLE 1.16

Write a condensed structural formula for the single carboxylic acid with the molecular formula $C_3H_6O_2$.

STRATEGY

First draw the carboxyl group and add the two remaining carbons. Finally, add the five remaining hydrogens in such a way that each carbon in the molecule has four bonds to it.

SOLUTION

See problems 1.53–1.56, 1.58, 1.59

PROBLEM 1.16

Write condensed structural formulas for the two carboxylic acids and four esters with the molecular formula $C_4H_8O_2$.

SUMMARY OF KEY QUESTIONS

1.1 How Do We Describe the Electronic Structure of Atoms?

- An atom consists of a small, dense nucleus and electrons concentrated about the nucleus in regions of space called **shells**.
- Each shell can contain as many as $2n^2$ electrons, where n is the number of the shell. Each shell is subdivided into regions of space called **orbitals**.
- The first shell ($n = 1$) has a single s orbital and can hold $2 \times 1^2 = 2$ electrons.
- The second shell ($n = 2$) has one s orbital and three p orbitals and can hold $2 \times 2^2 = 8$ electrons.
- The **Lewis structure** of an element shows the symbol of the element surrounded by a number of dots equal to the number of electrons in its **valence shell**.

1.2 What Is the Lewis Model of Bonding?

- According to the **Lewis model of bonding**, atoms bond together in such a way that each atom participating in a chemical bond acquires a completed valence-shell electron configuration resembling that of the noble gas nearest it in atomic number.
- Atoms that lose sufficient electrons to acquire a completed valence shell become **cations**; atoms that gain sufficient electrons to acquire a completed valence shell become **anions**.
- An **ionic bond** is a chemical bond formed by the attractive force between an anion and a cation.
- A **covalent bond** is a chemical bond formed by the sharing of electron pairs between atoms.
- The tendency of main-group elements (those of Groups 1A–7A) to achieve an outer shell of eight **valence electrons** is called the **octet rule**.
- **Electronegativity** is a measure of the force of attraction by an atom for electrons it shares in a chemical bond with another atom. Electronegativity increases from left to right and from bottom to top in the Periodic Table.
- A **Lewis structure** for a molecule or an ion must show (1) the correct arrangement of atoms, (2) the correct number of valence electrons, (3) no more than two electrons in the outer shell of hydrogen, (4) no more than eight electrons in the outer shell of any second-period element, and (5) all formal charges.
- **Formal charge** is the charge on an atom in a molecule or polyatomic ion.

1.3 How Do We Predict Bond Angles and the Shapes of Molecules?

- **Valence-shell electron pair repulsion (VSEPR)** predicts bond angles of 109.5° about atoms surrounded by four regions of electron density, bond angles of 120° about atoms surrounded by three regions of electron density, and bond angles of 180° about atoms surrounded by two regions of electron density.
- The common shapes of small molecules include **tetrahedral, pyramidal, linear**, and **bent**.

1.4 How Do We Predict If a Molecule Is Polar or Nonpolar?

- As a rough guideline, we say that a **nonpolar covalent bond** is a covalent bond in which the difference in electronegativity between the bonded atoms is less than 0.5 unit.
- A **polar covalent bond** is a covalent bond in which the difference in electronegativity between the bonded atoms is between 0.5 and 1.9 units. In a polar covalent bond, the more electronegative atom bears a partial negative charge ($\delta-$) and the less electronegative atom bears a partial positive charge ($\delta+$).
- A molecule is polar if the vector sum of its bond **dipoles** equals non-zero.
- A molecule is nonpolar if (1) it has all nonpolar bonds, or (2) it has polar bonds and the vector sum of its bond dipoles is zero (i.e., the bond dipoles cancel each other).

1.5 What Is Resonance?

- According to the **theory of resonance**, a molecule or ion for which no single Lewis structure is adequate is best described by writing two or more **resonance contributing structures** and considering the real molecule or ion to be a **hybrid** of the various contributing structures.
- Resonance contributing structures are interconnected by **double-headed arrows**.
- We show how valence electrons are redistributed from one contributing structure to the next by **curved arrows**. A curved arrow extends from where the electrons are initially shown (on an atom or in a covalent bond) to their new location (an adjacent atom or an adjacent covalent bond).
- The use of curved arrows in this way is commonly referred to as **electron pushing**.

1.6 What Is the Orbital Overlap Model of Covalent Bonding?

- According to the **orbital overlap model**, the formation of a covalent bond results from the overlap of **atomic orbitals**.
- The greater the overlap, the stronger is the resulting covalent bond.
- The combination of atomic orbitals is called **hybridization**, and the resulting orbitals are called **hybrid orbitals**.
- The combination of one 2*s* atomic orbital and three 2*p* atomic orbitals produces four equivalent ***sp*^{3} hybrid orbitals**, each pointing toward a corner of a regular tetrahedron at angles of 109.5°.
- The combination of one 2*s* atomic orbital and two 2*p* atomic orbitals produces three equivalent ***sp*^{2} hybrid orbitals**, the axes of which lie in a plane at angles of 120°. Most C═C, C═O, and C═N **double bonds** are a combination of one **sigma (σ) bond** formed by the overlap of ***sp*^{2} hybrid orbitals** and one **pi (π) bond** formed by the overlap of parallel 2*p* atomic orbitals.
- The combination of one 2*s* atomic orbital and one 2*p* atomic orbital produces two equivalent ***sp* hybrid orbitals**, the axes of which lie in a plane at an angle of 180°.
- All C≡C triple bonds are a combination of one sigma bond formed by the overlap of *sp* hybrid orbitals and two pi bonds formed by the overlap of two pairs of parallel 2*p* atomic orbitals.
- Hybrid orbitals can be arranged in tetrahedral, **trigonal planar**, and linear geometries.

1.7 What Are Functional Groups?

- **Functional groups** are characteristic structural units by which we divide organic compounds into classes and that serve as a basis for nomenclature. They are also sites of chemical reactivity; a particular functional group, in whatever compound we find it, undergoes the same types of reactions.
- Important functional groups for us at this stage in the course are
  - the **hydroxyl group** of **1°**, **2°**, and **3° alcohols**
  - the **amino group** of **1°**, **2°**, and **3° amines**
  - the **carbonyl group** of **aldehydes** and **ketones**
  - the **carboxyl group** of **carboxylic acids**

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. These bonds are arranged in order of increasing polarity C—H < N—H < O—H. (1.2)
2. All atoms in a contributing structure must have complete valence shells. (1.5)
3. An electron in a 1*s* orbital is held closer to the nucleus than an electron in a 2*s* orbital. (1.1)
4. A sigma bond and a pi bond have in common that each can result from the overlap of atomic orbitals. (1.6)

5. The molecular formula of the smallest aldehyde is C_3H_6O, and that of the smallest ketone is also C_3H_6O. (1.7)

6. To predict whether a covalent molecule is polar or nonpolar, you must know both the polarity of each covalent bond and the geometry (shape) of the molecule. (1.4)

7. An orbital is a region of space that can hold two electrons. (1.1)

8. In the ground-state electron configuration of an atom, only the lowest-energy orbitals are occupied. (1.1)

9. Electronegativity generally increases with atomic number. (1.2)

10. Paired electron spins means that the two electrons are aligned with their spins North Pole to North Pole and South Pole to South Pole. (1.1)

11. According to the Lewis model of bonding, atoms bond together in such a way that each atom participating in the bond acquires an outer-shell electron configuration matching that of the noble gas nearest it in atomic number. (1.2)

12. A primary amine contains one N—H bond, a secondary amine contains two N—H bonds, and a tertiary amine contains three N—H bonds. (1.7)

13. All bond angles in sets of resonance contributing structures must be the same. (1.5)

14. Electronegativity is a measure of an atom's attraction for electrons it shares in a chemical bond with another atom. (1.2)

15. An orbital can hold a maximum of two electrons with their spins paired. (1.1)

16. Fluorine in the upper right corner of the Periodic Table is the most electronegative element; hydrogen, in the upper left corner, is the least electronegative element. (1.2)

17. A primary alcohol has one —OH group, a secondary alcohol has two —OH groups, and a tertiary alcohol has three —OH groups. (1.7)

18. H_2O and NH_3 are polar molecules, but CH_4 is nonpolar. (1.4)

19. Electronegativity generally increases from top to bottom in a column of the Periodic Table. (1.2)

20. All contributing structures must have the same number of valence electrons. (1.5)

21. A carbon–carbon double bond is formed by the overlap of sp^2 hybrid orbitals, and a triple bond is formed by the overlap of sp^3 hybrid orbitals. (1.6)

22. A covalent bond formed by sharing two electrons is called a double bond. (1.2)

23. The functional groups of an alcohol, an aldehyde, and a ketone have in common the fact that each contains a single oxygen atom. (1.7)

24. Electrons in atoms are confined to regions of space called principal energy levels. (1.1)

25. In a single bond, two atoms share one pair of electrons; in a double bond, they share two pairs of electrons; and in a triple bond, they share three pairs of electrons. (1.2)

26. The Lewis structure for ethene, C_2H_4, must show eight valence electrons. (1.2)

27. The Lewis structure for formaldehyde, CH_2O, must show eight valence electrons. (1.2)

28. The letters VSEPR stand for valence-shell electron pair repulsion. (1.3)

29. In predicting bond angles about a central atom in a covalent bond, VSEPR considers only shared pairs (pairs of electrons involved in forming covalent bonds). (1.3)

30. An *sp* hybrid orbital may contain a maximum of four electrons, an sp^2 hybrid orbital may contain a maximum of six valence electrons, and an sp^3 hybrid orbital may contain a maximum of eight electrons. (1.6)

31. For a central atom surrounded by three regions of electron density, VSEPR predicts bond angles of 360°/3 = 120°. (1.3)

32. The three 2*p* orbitals are aligned parallel to each other. (1.1)

33. All molecules with polar bonds are polar. (1.4)

34. Electronegativity generally increases from left to right across a period of the Periodic Table. (1.2)

35. A compound with the molecular formula C_3H_6O may be an aldehyde, a ketone, or a carboxylic acid. (1.7)

36. Dichloromethane, CH_2Cl_2 is polar, but tetrachloromethane, CCl_4, is nonpolar. (1.4)

37. A covalent bond is formed between atoms whose difference in electronegativity is less than 1.9. (1.2)

38. Each principal energy level can hold two electrons. (1.1)

39. Atoms that share electrons to achieve filled valence shells form covalent bonds. (1.2)

40. Contributing structures differ only in the distribution of valence electrons. (1.5)

41. In creating hybrid orbitals (*sp*, sp^2, and sp^3), the number of hybrid orbitals created is equal to the number of atomic orbitals hybridized. (1.6)

42. VSEPR treats the two electron pairs of a double bond and the three electron pairs of a triple bond as one region of electron density. (1.3)

43. If the difference in electronegativity between two atoms is zero (they have identical electronegativities), then the two atoms will not form a covalent bond. (1.2)

44. A carbon–carbon triple bond is a combination of one sigma bond and two pi bonds. (1.6)

45. A carbon–carbon double bond is a combination of two sigma bonds. (1.6)

46. An *s* orbital has the shape of a sphere with the center of the sphere at the nucleus. (1.1)

47. A functional group is a group of atoms in an organic molecule that undergoes a predictable set of chemical reactions. (1.7)

48. In a polar covalent bond, the more electronegative atom has a partial negative charge (δ–) and the less electronegative atom has a partial positive charge (δ+). (1.2)

49. Electronegativity depends on both the nuclear charge and the distance of the valence electrons from the nucleus. (1.2)

50. There are two alcohols with the molecular formula C_3H_8O. (1.7)

51. In methanol, CH_3OH, the O—H bond is more polar than the C—O bond. (1.4)

52. The molecular formula of the smallest carboxylic acid is $C_2H_6O_2$. (1.7)

53. Each 2*p* orbital has the shape of a dumbbell with the nucleus at the midpoint of the dumbbell. (1.1)

54. Atoms that lose electrons to achieve a filled valence shell become cations and form ionic bonds with anions. (1.1)

55. There are three amines with the molecular formula C_3H_9N. (1.7)

Answers: (1) T (2) F (3) T (4) T (5) F (6) T (7) T (8) T (9) F (10) F (11) T (12) F (13) F (14) T (15) T (16) F (17) F (18) T (19) F (20) T (21) F (22) F (23) T (24) T (25) T (26) F (27) F (28) T (29) F (30) F (31) T (32) F (33) F (34) T (35) F (36) T (37) T (38) F (39) T (40) T (41) T (42) T (43) F (44) T (45) F (46) T (47) T (48) T (49) F (50) T (51) T (52) F (53) T (54) T (55) F

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 1.1 Electronic Structure of Atoms

1.17 Write the ground-state electron configuration for each element: **(See Example 1.1)**

(a) Sodium
(b) Magnesium
(c) Oxygen
(d) Nitrogen
(e) Potassium
(f) Aluminum
(g) Phosphorus
(h) Argon

1.18 Write the ground-state electron configuration for each ion: **(See Example 1.1)**

(a) Na^+
(b) Cl^-
(c) Mg^{2+}
(d) H^+
(e) H^-
(f) K^+
(g) Br^+
(h) Li^+

1.19 Which element has the ground-state electron configuration **(See Example 1.1)**

(a) $1s^2 2s^2 2p^6 3s^2 3p^4$
(b) $1s^2 2s^2 2p^4$
(c) $[He]2s^2 2p^2$
(d) $[Ne]3s^2 3p^5$

1.20 Which element or ion does not have the ground-state electron configuration $1s^2 2s^2 2p^6 3s^2 3p^6$? **(See Example 1.1)**

(a) S^{2-}
(b) Cl^-
(c) Ar
(d) Ca^{2+}
(e) K

1.21 Define *valence shell* and *valence electron*. Why are valence electrons more important to bonding than other types of electrons?

1.22 How many electrons are in the valence shell of each element? **(See Example 1.2)**

(a) Carbon
(b) Nitrogen
(c) Chlorine
(d) Aluminum
(e) Oxygen
(f) Silicon

1.23 How many electrons are in the valence shell of each ion? **(See Example 1.2)**

(a) H^+ (b) H^- (c) F^- (d) Cl^+ (e) S^{2-}

SECTION 1.2 Lewis Structures

1.24 Judging from their relative positions in the Periodic Table, which element in each set is more electronegative? **(See Example 1.3)**

(a) Carbon or nitrogen
(b) Chlorine or bromine
(c) Oxygen or sulfur
(d) Oxygen or phosphorus

1.25 Which compounds have nonpolar covalent bonds, which have polar covalent bonds, and which have ionic bonds? **(See Example 1.4)**

(a) LiF (b) CH_3F (c) $MgCl_2$ (d) HCl

1.26 Using the symbols δ– and δ+, indicate the direction of polarity, if any, in each covalent bond: **(See Example 1.5)**

(a) C—Cl
(b) S—H
(c) C—S
(d) P—H

1.27 Write Lewis structures for each of the following compounds, showing all valence electrons (none of the compounds contains a ring of atoms): **(See Example 1.6)**

(a) Hydrogen peroxide, H_2O_2
(b) Hydrazine, N_2H_4
(c) Methanol, CH_3OH
(d) Methanethiol, CH_3SH
(e) Methanamine, CH_3NH_2
(f) Chloromethane, CH_3Cl
(g) Dimethyl ether, CH_3OCH_3
(h) Ethane, C_2H_6
(i) Ethylene, C_2H_4
(j) Acetylene, C_2H_2
(k) Carbon dioxide, CO_2
(l) Formaldehyde, CH_2O
(m) Acetone, CH_3COCH_3
(n) Carbonic acid, H_2CO_3
(o) Acetic acid, CH_3COOH

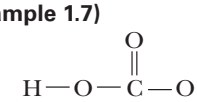
1.28 Write Lewis structures for these ions: **(See Example 1.6)**

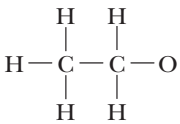
(a) Bicarbonate ion, HCO_3^-
(b) Carbonate ion, CO_3^{2-}
(c) Acetate ion, CH_3COO^-
(d) Chloride ion, Cl^-

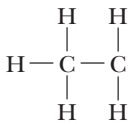
1.29 Why are the following molecular formulas impossible?

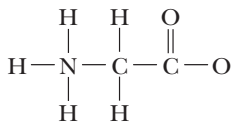
(a) CH_5 (b) C_2H_7 (c) H_2^{2+} (d) HN^{3-}

1.30 Following the rule that each atom of carbon, oxygen, and nitrogen reacts to achieve a complete outer shell of eight valence electrons, add unshared pairs of electrons as necessary to complete the valence shell of each atom in the following ions. Then, assign formal charges as appropriate: **(See Example 1.7)**

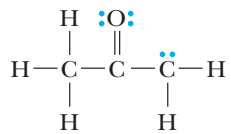
(a) 

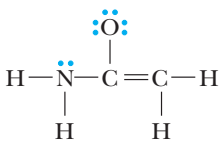
(b) 

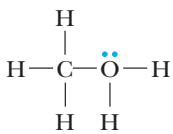
(c) 

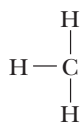
(d) 

1.31 The following Lewis structures show all valence electrons. Assign formal charges in each structure as appropriate. **(See Example 1.7)**

(a) 

(b) 

(c) 

(d) 

1.32 Each compound contains both ionic and covalent bonds. Draw a Lewis structure for each, and show by charges which bonds are ionic and by dashes which bonds are covalent. **(See Example 1.7)**

(a) NaOH
(b) $NaHCO_3$
(c) NH_4Cl
(d) CH_3COONa
(e) CH_3ONa
(f) KCN

1.33 Silver and oxygen can form a stable compound. Predict the formula of this compound, and state whether the compound consists of ionic or covalent bonds.

1.34 Draw Lewis structures for the following molecule and ions: **(See Example 1.7)**

(a) NH_3
(b) NH_4^+
(c) NH_2^-
(d) CH_3^+

SECTION 1.2 Polarity of Covalent Bonds

1.35 Which statement is true about electronegativity?

(a) Electronegativity increases from left to right in a period of the Periodic Table.
(b) Electronegativity increases from top to bottom in a column of the Periodic Table.
(c) Hydrogen, the element with the lowest atomic number, has the smallest electronegativity.
(d) The higher the atomic number of an element, the greater is its electronegativity.

1.36 Why does fluorine, the element in the upper right corner of the Periodic Table, have the largest electronegativity of any element?

1.37 Arrange the single covalent bonds within each set in order of increasing polarity:

(a) C—H, O—H, N—H
(b) C—H, C—Cl, C—I
(c) C—C, C—O, C—N
(d) C—Li, C—Hg, C—Mg

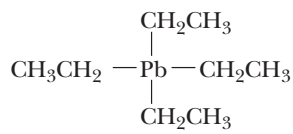
1.38 Using the values of electronegativity given in Table 1.4, predict which indicated bond in each set is more polar and, using the symbols $\delta+$ and $\delta-$, show the direction of its polarity: **(See Example 1.5)**

(a) CH_3—OH or CH_3O—H
(b) H—NH_2 or CH_3—NH_2
(c) CH_3—SH or CH_3S—H
(d) CH_3—F or H—F
(e) H_2C=NH or H_2C=O
(f) H_2B—H or F_2B—F
(g) H_2C=O or H_2C=S
(h) CH_3—MgBr or CH_3—Li

1.39 Identify the most polar bond in each molecule:

(a) $HSCH_2CH_2OH$
(b) $CHCl_2F$
(c) $HOCH_2CH_2NH_2$
(d) CH_3OCH_2OH
(e) HOCl
(f) $CH_3NCHCHO$

1.40 Predict whether the carbon–metal bond in each of these organometallic compounds is nonpolar covalent, polar covalent, or ionic. For each polar covalent bond, show its direction of polarity using the symbols δ+ and δ–. **(See Example 1.5)**

(a) 

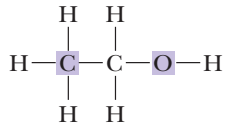
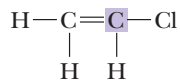
Tetraethyllead

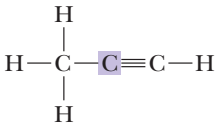
(b) CH_3—Mg—Cl
Methylmagnesium chloride

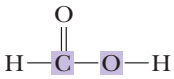
(c) CH_3—Hg—CH_3
Dimethylmercury

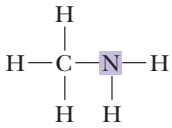
SECTION 1.3 Bond Angles and Shapes of Molecules

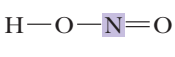
1.41 Using VSEPR, predict bond angles about each highlighted atom: **(See Example 1.8)**

(a)  (b) 

(c) 

(d) 

(e) 

(f) 

1.42 Using VSEPR, predict bond angles about each atom of carbon, nitrogen, and oxygen in these molecules. (*Hint*: First add unshared pairs of electrons as necessary to complete the valence shell of each atom, and then make your predictions of bond angles.) **(See Example 1.8)**

(a) $CH_3—CH_2—CH_2—OH$

(b) $CH_3—CH_2—C(=O)—H$

(c) $CH_3—CH=CH_2$

(d) $CH_3—C\equiv C—CH_3$

(e) $CH_3—C(=O)—O—CH_3$

(f) $CH_3—N(CH_3)—CH_3$

1.43 Silicon is immediately below carbon in the Periodic Table. Predict the C—Si—C bond angle in tetramethylsilane, $(CH_3)_4Si$. **(See Example 1.8)**

SECTION 1.4 Polar and Nonpolar Molecules

1.44 Draw a three-dimensional representation for each molecule. Indicate which molecules are polar and the direction of their polarity: **(See Example 1.9)**

(a) CH_3F (d) CCl_4 (g) $CH_3C\equiv N$

(b) CH_2Cl_2 (e) $CH_2=CCl_2$ (h) $(CH_3)_2C=O$

(c) $CHCl_3$ (f) $CH_2=CHCl$ (i) $N(CH_3)_3$

***1.45** Tetrafluoroethylene, C_2F_4, is the starting material for the synthesis of the polymer poly(tetrafluoroethylene), commonly known as Teflon. Molecules of tetrafluoroethylene are nonpolar. Propose a structural formula for this compound.

***1.46** Until several years ago, the two chlorofluorocarbons (CFCs) most widely used as heat-transfer media for refrigeration systems were Freon-11 (trichlorofluoromethane, CCl_3F) and Freon-12 (dichlorodifluoromethane, CCl_2F_2). Draw a three-dimensional representation of each molecule, and indicate the direction of its polarity. **(See Example 1.9)**

SECTION 1.5 Resonance Contributing Structures

1.47 Which of these statements are true about resonance contributing structures? **(See Example 1.10)**

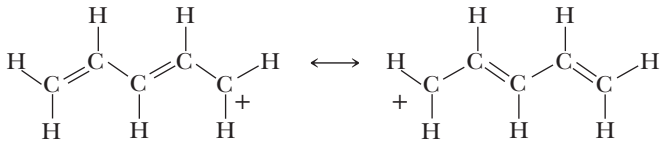
(a) All contributing structures must have the same number of valence electrons.

(b) All contributing structures must have the same arrangement of atoms.

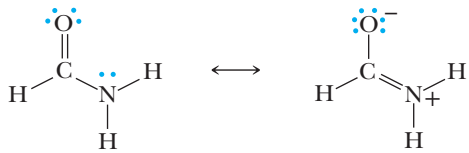
(c) All atoms in a contributing structure must have complete valence shells.

(d) All bond angles in sets of contributing structures must be the same.

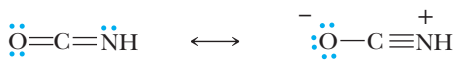
(e) The following pair represents acceptable resonance contributing structures:



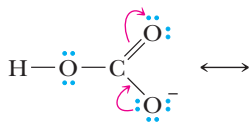
(f) The following pair represents acceptable resonance contributing structures:

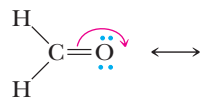


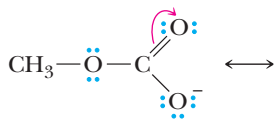
(g) The following pair represents acceptable resonance contributing structures:

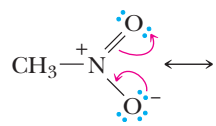


1.48 Draw the resonance contributing structure indicated by the curved arrow(s), and assign formal charges as appropriate: **(See Example 1.11)**

(a) 

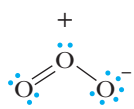
(b) 

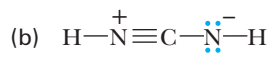
(c) 

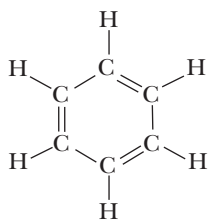
(d) 

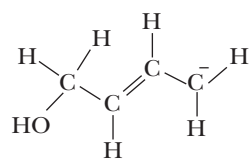
1.49 Using VSEPR, predict the bond angles about the carbon atom in each pair of contributing structures in Problem 1.48. In what way do the bond angles change from one contributing structure to the other?

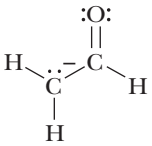
1.50 Draw acceptable resonance contributing structure(s) for each of the compounds shown. **(See Example 1.11)**

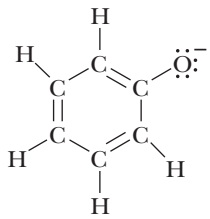
(a) 

(b) 

(c) 

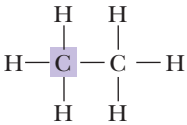
(d) 

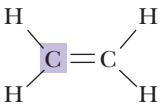
(e) 

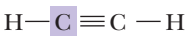
(f) 

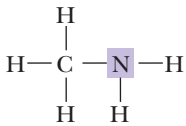
SECTION 1.6 Hybridization of Atomic Orbitals

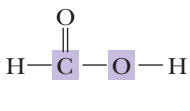
1.51 State the hybridization of each highlighted atom: **(See Example 1.12)**

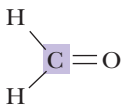
(a) 

(b) 

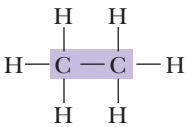
(c) 

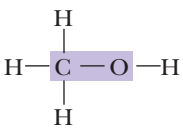
(d) 

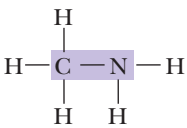
(e) 

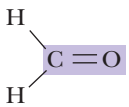
(f) 

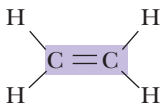
1.52 Describe each highlighted bond by indicating the type of bond(s) and the hybridization of the highlighted atoms: **(See Example 1.12)**

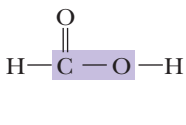
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

SECTION 1.7 Functional Groups

1.53 Draw Lewis structures for these functional groups. Be certain to show all valence electrons on each: **(See Examples 1.13–1.16)**

(a) Carbonyl group
(b) Carboxyl group
(c) Hydroxyl group
(d) Primary amino group

1.54 Draw the structure for a compound with the molecular formula **(See Examples 1.13–1.16)**

(a) C_2H_6O that is an alcohol.
(b) C_3H_6O that is an aldehyde.
(c) C_3H_6O that is a ketone.
(d) $C_3H_6O_2$ that is a carboxylic acid.
(e) $C_4H_{11}N$ that is a tertiary amine.

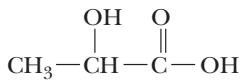
1.55 Draw condensed structural formulas for all compounds with the molecular formula C_4H_8O that contain **(See Examples 1.13–1.16)**

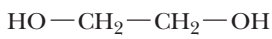
(a) a carbonyl group. (There are two aldehydes and one ketone.)
(b) a carbon–carbon double bond and a hydroxyl group. (There are eight.)

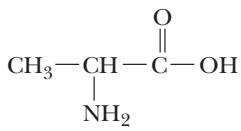
1.56 Draw structural formulas for **(See Examples 1.13–1.16)**

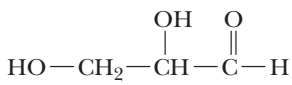
(a) the eight alcohols with the molecular formula $C_5H_{12}O$.
(b) the eight aldehydes with the molecular formula $C_6H_{12}O$.
(c) the six ketones with the molecular formula $C_6H_{12}O$.
(d) the eight carboxylic acids with the molecular formula $C_6H_{12}O_2$.
(e) the three tertiary amines with the molecular formula $C_5H_{13}N$.

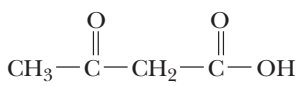
***1.57** Identify the functional groups in each compound (we study each compound in more detail in the indicated section):

(a) 
Lactic acid
(Section 21.4A)

(b) 
Ethylene glycol
(Section 8.2C)

(c) 
Alanine
(Section 18.2B)

(d) 
Glyceraldehyde
(Section 17.2A)

(e) 
Acetoacetic acid
(Section 13.2B)

(f) $H_2NCH_2CH_2CH_2CH_2CH_2CH_2NH_2$
1,6-Hexanediamine
(Section 16.4A)

***1.58** Dihydroxyacetone, $C_3H_6O_3$, the active ingredient in many sunless tanning lotions, contains two 1° hydroxyl groups, each on a different carbon, and one ketone group. Draw a structural formula for dihydroxyacetone. **(See Examples 1.13–1.16)**

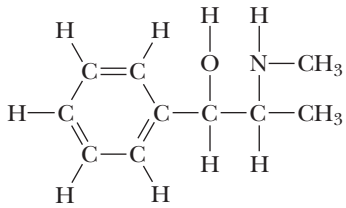
***1.59** Propylene glycol, $C_3H_8O_2$, commonly used in airplane deicers, contains a 1° alcohol and a 2° alcohol. Draw a structural formula for propylene glycol. **(See Examples 1.13–1.16)**

***1.60** Ephedrine is a molecule found in the dietary supplement ephedra, which has been linked to adverse health reactions such as heart attacks, strokes, and heart palpitations. The use of ephedra in dietary supplements is now banned by the FDA.

(a) Identify at least two functional groups in ephedrine.

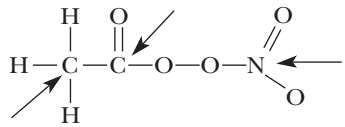
(b) Would you predict ephedrine to be polar or nonpolar?

Ephedrine



***1.61** Ozone (O_3) and carbon dioxide (CO_2) are both known as greenhouse gases. Compare and contrast their shapes, and indicate the hybridization of each atom in the two molecules.

***1.62** In the lower atmosphere that is also contaminated with unburned hydrocarbons, NO_2 participates in a series of reactions. One product of these reactions is peroxyacetyl nitrate (PAN). The connectivity of the atoms in PAN appears below.



(a) Determine the number of valence electrons in this molecule, and then complete its Lewis structure.

(b) Give the approximate values of the bond angles around each atom indicated with an arrow.

LOOKING AHEAD

1.63 Allene, C_3H_4, has the structural formula $H_2C{=}C{=}CH_2$. Determine the hybridization of each carbon in allene and predict the shape of the molecule.

1.64 Dimethylsulfoxide, $(CH_3)_2SO$, is a common solvent used in organic chemistry.

(a) Write a Lewis structure for dimethylsulfoxide.

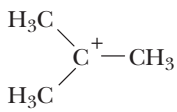
(b) Predict the hybridization of the sulfur atom in the molecule.

(c) Predict the geometry of dimethylsulfoxide.

(d) Is dimethylsulfoxide a polar or a nonpolar molecule?

1.65 In Chapter 5, we study a group of organic cations called carbocations. Following is the structure of one such carbocation, the *tert*-butyl cation:

tert-Butyl cation



(a) How many electrons are in the valence shell of the carbon bearing the positive charge?

(b) Predict the bond angles about this carbon.

(c) Given the bond angles you predicted in (b), what hybridization do you predict for this carbon?

1.66 We also study the isopropyl cation, $(CH_3)_2CH^+$, in Chapter 5.

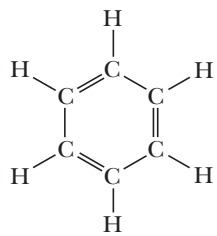
(a) Write a Lewis structure for this cation. Use a plus sign to show the location of the positive charge.

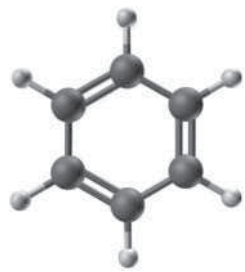
(b) How many electrons are in the valence shell of the carbon bearing the positive charge?

(c) Use VSEPR to predict all bond angles about the carbon bearing the positive charge.

(d) Describe the hybridization of each carbon in this cation.

1.67 In Chapter 9, we study benzene, C_6H_6, and its derivatives.



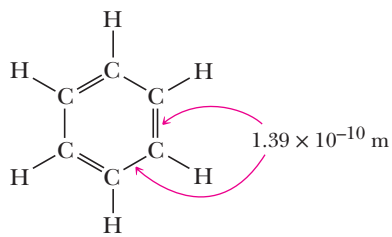


(a) Predict each H—C—C and each C—C—C bond angle on benzene.

(b) State the hybridization of each carbon in benzene.

(c) Predict the shape of a benzene molecule.

1.68 Explain why all the carbon–carbon bonds in benzene are equal in length.

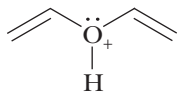


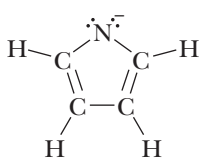
GROUP LEARNING ACTIVITIES

Studies have shown that working in groups enhances learning and fosters camaraderie. The following problems represent activities that you can do in groups of two or more.

1.69 Take turns by naming a functional group and challenging each other to draw an organic molecule with at least three carbon atoms that contains that functional group.

1.70 Draw all possible contributing structures for the molecules shown. Then discuss which of these contributing structures would not contribute significantly to the resonance hybrid. Provide good reasons for the structures you eliminate.

(a) 

(b) 

1.71 Refer to the list of functional groups on page I.10 at the end of this text. Take turns choosing one of the examples in the list and indicate the hybridization of each C, O, N, or S atom in the example.

1.72 Rank the three types of hybridized orbitals (*sp*, sp^2, and sp^3) from most fitting to least fitting of the following characteristics. Provide reasons for your ranking.

(a) Most *s* character

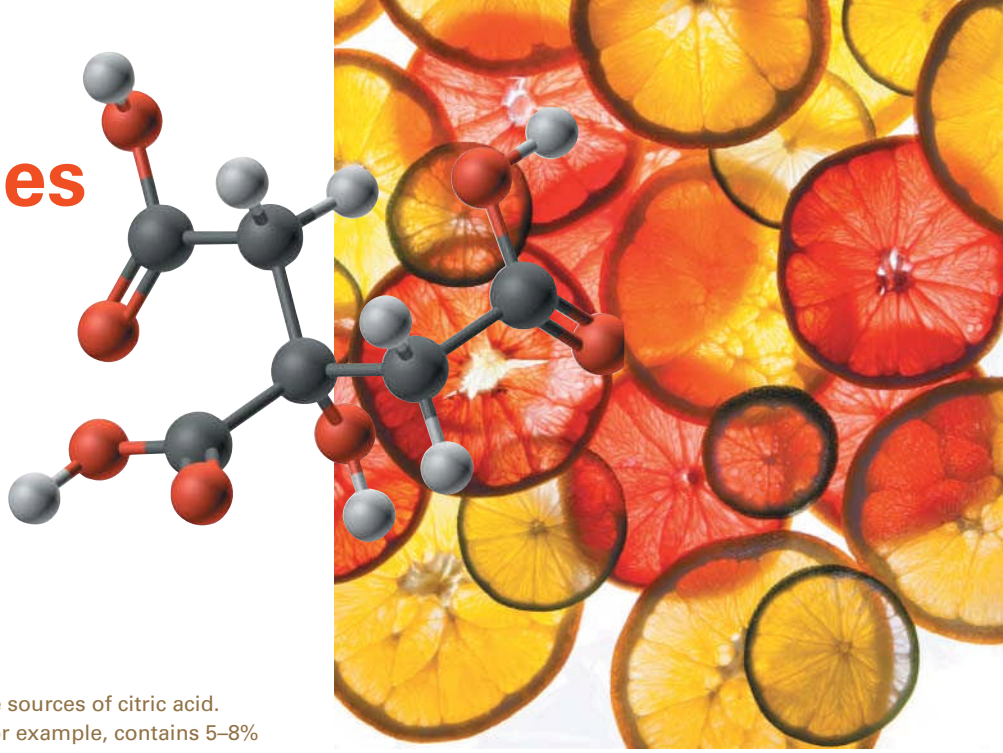
(b) Highest in energy

(c) Forms the longest sigma bonds

1.73 Using the valence-shell electron pair model, predict the geometry and bond angles present in each of these molecules.

(a) XeF_4 (b) PCl_5 (c) SF_6

Acids and Bases



2

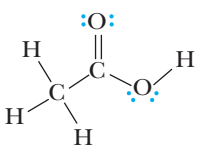
Citrus fruits are sources of citric acid. Lemon juice, for example, contains 5–8% citric acid. Inset: A model of citric acid.

KEY QUESTIONS

HOW TO

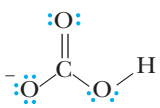
DID YOU KNOW THAT ACETIC ACID IS ONE OF THE STRONGER ORGANIC ACIDS, yet it is often consumed by humans in the form of vinegar? Would it surprise you to learn that hydrochloric acid, one of the strongest acids known, exists in abundance in the stomach of most mammals and that bicarbonate, a weak base with a structure and reactivity analogous to acetic acid, is responsible for protecting our stomachs from being auto-digested by its hydrochloric acid? Did you know that we can predict the relative strengths of many acids and bases just by comparing their chemical structures?

In this chapter, we will study the acid–base properties of the major classes of organic compounds. It is through our understanding of the fundamentals of acid–base chemistry that we can begin to answer these questions and comprehend the majority of the reactions that we will study in this course.



acetic acid

hydrochloric acid



bicarbonate

2.1 What Are Arrhenius Acids and Bases?

The first useful definitions of an **acid** and a **base** were put forward by Svante Arrhenius (1859–1927) in 1884; Nobel Prize in Chemistry 1903. According to the original Arrhenius definitions, an acid is a substance that dissolves in water to produce H^+ ions, and a base is a substance that dissolves in water to produce OH^- ions. Today we know that a H^+ ion does not exist in water because it reacts immediately with an H_2O molecule to give a hydronium ion, H_3O^+:

Arrhenius acid A substance that dissolves in water to produce H^+ ions.

Arrhenius base A substance that dissolves in water to produce OH^- ions.

$$H^+(aq) + H_2O(l) \longrightarrow \underset{\text{Hydronium ion}}{H_3O^+(aq)}$$

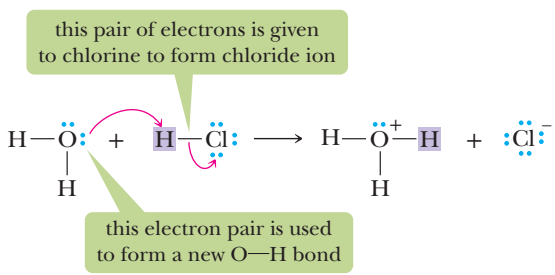
Apart from this modification, the Arrhenius definitions of acid and base are still valid and useful today, as long as we are talking about aqueous solutions. However, the Arrhenius concept of acids and bases is so intimately tied to reactions that take place in water that it has no good way to deal with acid–base reactions in nonaqueous solutions. For this reason, we concentrate in this chapter on the Brønsted–Lowry definitions of acids and bases, which are more useful to us in our discussion of reactions of organic compounds.

HOW TO 2.1 Use Curved Arrows to Show the Transfer of a Proton from an Acid to a Base

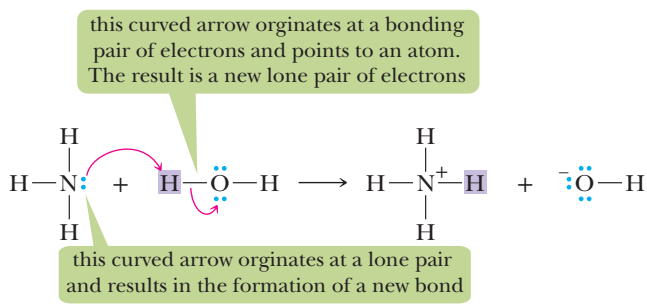
We can show the transfer of a proton from an acid to a base by using a symbol called a **curved arrow.** Curved arrows will be used throughout your study of organic chemistry to describe how reactions proceed. Therefore, it is very important that you become proficient in their use.

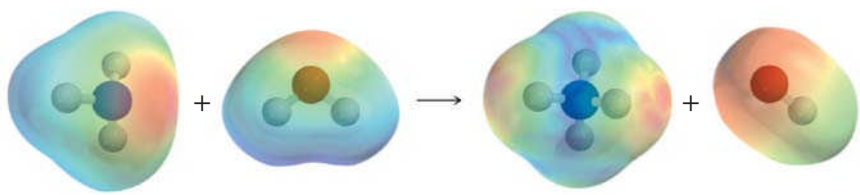
1. Write the Lewis structure of each reactant and product, showing all valence electrons on reacting atoms.
2. Use curved arrows to show the change in position of electron pairs during the reaction. The tail of the curved arrow is located at an electron pair. The head of the curved arrow shows the new position of the electron pair.
3. A change in position of an electron pair originating from an atom will form a new bond to that atom, while a change in position of an electron pair originating from a bond will result in breaking that bond.

EXAMPLE 1



EXAMPLE 2





Notice the increase in charge distribution upon protonation of NH_2 and deprotonation of H_2O. The nitrogen of NH_4^+ shows a more intense blue than the nitrogen of NH_2, and the oxygen of OH^- shows a more intense red than the oxygen of H_2O.

2.2 What Are Brønsted–Lowry Acids and Bases?

Brønsted–Lowry acid A proton donor.

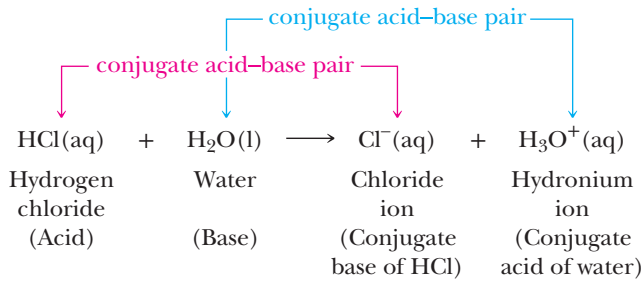
Brønsted–Lowry base A proton acceptor.

Conjugate base The species formed when an acid donates a proton.

Conjugate acid The species formed when a base accepts a proton.

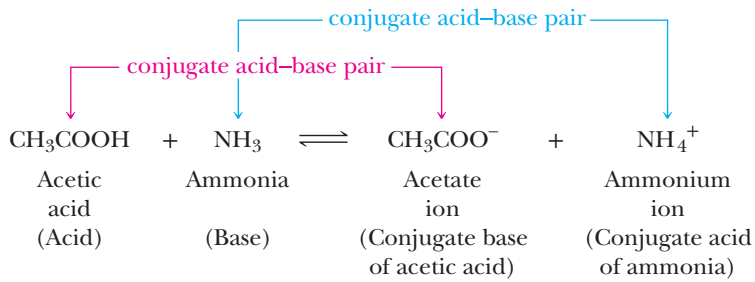
In 1923, the Danish chemist Johannes Brønsted and the English chemist Thomas Lowry independently proposed the following definitions: An **acid** is a **proton donor**, a **base** is a **proton acceptor**, and an acid–base reaction is a **proton-transfer reaction**. Furthermore, according to the Brønsted–Lowry definitions, any pair of molecules or ions that can be interconverted by the transfer of a proton is called a **conjugate acid–base pair**. When an acid transfers a proton to a base, the acid is converted to its **conjugate base**. When a base accepts a proton, the base is converted to its **conjugate acid**.

We can illustrate these relationships by examining the reaction of hydrogen chloride with water to form chloride ion and hydronium ion:

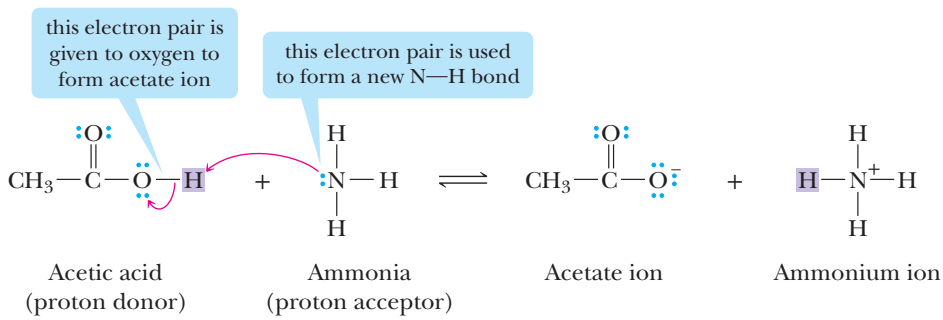


In this reaction, the acid HCl donates a proton and is converted to its conjugate base, Cl^-. The base H_2O accepts a proton and is converted to its conjugate acid, H_3O^+.

We have illustrated the application of the Brønsted–Lowry definitions with water as a reactant. These definitions, however, do not require water as a reactant. Consider the following reaction between acetic acid and ammonia:



We can use curved arrows to show how this reaction takes place:



The rightmost curved arrow shows that the unshared pair of electrons on nitrogen becomes shared between N and H to form a new H—N bond. At the same time that the H—N bond forms, the O—H bond breaks, and the electron pair of the O—H bond moves entirely to oxygen to form the $—O^-$ of the acetate ion. The result of these two electron-pair shifts is the transfer of a proton from an acetic acid molecule to an ammonia molecule. Table 2.1

gives examples of common acids and their conjugate bases. As you study the examples of conjugate acid–base pairs in the table, note the following points:

1. An acid can be positively charged, neutral, or negatively charged. Examples of these charge types are H_3O^+, H_2CO_3, and $H_2PO_4^-$.

2. A base can be negatively charged or neutral. Examples of these charge types are Cl^- and NH_3.

3. Acids are classified as monoprotic, diprotic, or triprotic, depending on the number of protons each may give up. Examples of **monoprotic acids** include HCl, HNO_3, and CH_3COOH. Examples of **diprotic acids** include H_2SO_4 and H_2CO_3. An example of a **triprotic acid** is H_3PO_4. Carbonic acid, for example, loses one proton to become bicarbonate ion and then a second proton to become carbonate ion:

$$\underset{\text{Carbonic acid}}{H_2CO_3} + H_2O \rightleftharpoons \underset{\text{Bicarbonate ion}}{HCO_3^-} + H_3O^+$$

$$\underset{\text{Bicarbonate ion}}{HCO_3^-} + H_2O \rightleftharpoons \underset{\text{Carbonate ion}}{CO_3^{2-}} + H_3O^+$$

4. Several molecules and ions appear in both the acid and conjugate base columns; that is, each can function as either an acid or a base. The bicarbonate ion, HCO_3^-, for example, can give up a proton to become CO_3^{2-} (in which case it is an acid) or it can accept a proton to become H_2CO_3 (in which case it is a base).

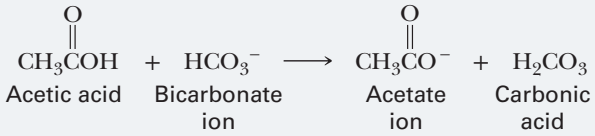
5. There is an inverse relationship between the strength of an acid and the strength of its conjugate base. **The stronger the acid, the weaker is its conjugate base.** HI, for example, is the strongest acid listed in Table 2.1, and I^-, its conjugate base, is the weakest base. As another example, CH_3COOH (acetic acid) is a stronger acid than H_2CO_3 (carbonic acid); conversely, CH_3COO^- (acetate ion) is a weaker base than HCO_3^- (bicarbonate ion).

TABLE 2.1 Some Acids and Their Conjugate Bases

	Acid	Name	Conjugate Base	Name	
Strong Acids	HI	hydroiodic acid	I^-	iodide ion	Weak Bases
	HCl	hydrochloric acid	Cl^-	chloride ion	
	H_2SO_4	sulfuric acid	HSO_4^-	hydrogen sulfate ion	
	HNO_3	nitric acid	NO_3^-	nitrate ion	
	H_3O^+	hydronium ion	H_2O	water	
	HSO_4^-	hydrogen sulfate ion	SO_4^{2-}	sulfate ion	
	H_3PO_4	phosphoric acid	$H_2PO_4^-$	dihydrogen phosphate ion	
	CH_3COOH	acetic acid	CH_3COO^-	acetate ion	
	H_2CO_3	carbonic acid	HCO_3^-	bicarbonate ion	
	H_2S	hydrogen sulfide	HS^-	hydrogen sulfide ion	
	$H_2PO_4^-$	dihydrogen phosphate ion	HPO_4^{2-}	hydrogen phosphate ion	
	NH_4^+	ammonium ion	NH_3	ammonia	
	HCN	hydrocyanic acid	CN^-	cyanide ion	
	C_6H_5OH	phenol	$C_6H_5O^-$	phenoxide ion	
	HCO_3^-	bicarbonate ion	CO_3^{2-}	carbonate ion	
	HPO_4^{2-}	hydrogen phosphate ion	PO_4^{3-}	phosphate ion	
Weak Acids	H_2O	water	OH^-	hydroxide ion	Strong Bases
	C_2H_5OH	ethanol	$C_2H_5O^-$	ethoxide ion	

EXAMPLE 2.1

Write the following acid–base reaction as a proton-transfer reaction. Label which reactant is the acid and which the base, as well as which product is the conjugate base of the original acid and which is the conjugate acid of the original base. Use curved arrows to show the flow of electrons in the reaction.

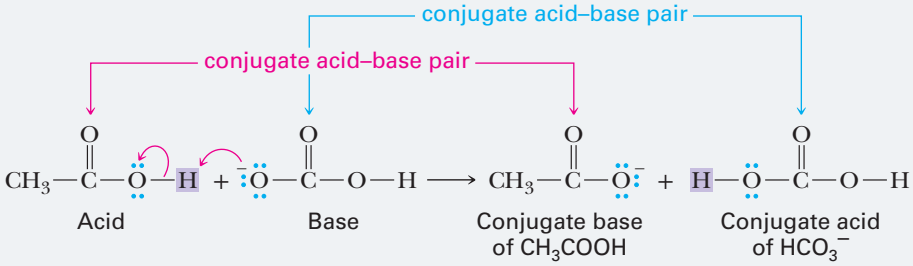


STRATEGY

First, write a Lewis structure for each reactant by showing all valence electrons on the reacting atoms: Acetic acid is the acid (proton donor), and bicarbonate ion is the base (proton acceptor). The members of a conjugate acid–base pair differ only by a proton, with the acid having the greater number of protons. To find the formula of the conjugate base, we remove one proton from the acid.

SOLUTION

From Table 2.1, we see that acetic acid is a stronger acid and, therefore, is the proton donor in this reaction.



See problems 2.7, 2.8

PROBLEM 2.1

Write each acid–base reaction as a proton-transfer reaction. Label which reactant is the acid and which product is the base, as well as which product is the conjugate base of the original acid and which is the conjugate acid of the original base. Use curved arrows to show the flow of electrons in each reaction.

(a) $CH_3SH + OH^- \longrightarrow CH_3S^- + H_2O$ **(b)** $CH_3OH + NH_2^- \longrightarrow CH_3O^- + NH_3$ **(c)** $H_2O + C_6H_5OH \longrightarrow H_3O^+ + C_6H_5O^-$

2.3 How Do We Measure the Strength of an Acid or Base?

Strong acid An acid that is completely ionized in aqueous solution.

Strong base A base that is completely ionized in aqueous solution.

Weak acid An acid that only partially ionizes in aqueous solution.

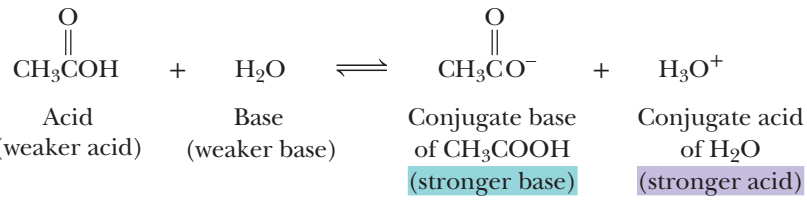
Weak base A base that only partially ionizes in aqueous solution.

A **strong acid** or **strong base** is one that ionizes completely in aqueous solution. When HCl is dissolved in water, a proton is transferred completely from HCl to H_2O to form Cl^- and H_3O^+. There is no tendency for the reverse reaction to occur—for the transfer of a proton from H_3O^+ to Cl^- to form HCl and H_2O. Therefore, when we compare the relative acidities of HCl and H_3O^+, we conclude that HCl is the stronger acid and H_3O^+ is the weaker acid. Similarly, H_2O is the stronger base and Cl^- is the weaker base.

Examples of strong acids in aqueous solution are HCl, HBr, HI, HNO_3, $HClO_4$, and H_2SO_4. Examples of strong bases in aqueous solution are LiOH, NaOH, KOH, $Ca(OH)_2$, and $Ba(OH)_2$.

A **weak acid** or **weak base** is one that only partially ionizes in aqueous solution. Most organic acids and bases are weak. Among the most common organic acids we deal with are

the carboxylic acids, which contain a carboxyl group, —COOH (Section 1.7D), as shown in the following reaction:



The equation for the ionization of a weak acid, HA, in water and the acid ionization constant K_a for this equilibrium are, respectively,

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ \qquad K_a = K_{eq}[H_2O] = \frac{[H_3O^+][A^-]}{[HA]}$$

Because acid ionization constants for weak acids are numbers with negative exponents, we often express them as $\mathbf{pK_a} = -\log_{10} K_a$. Table 2.2 gives the names, molecular formulas, and values of pK_a for some organic and inorganic acids. Note that the larger the value of pK_a, the weaker is the acid. Also note the inverse relationship between the strengths of the conjugate acid–base pairs; the stronger the acid, the weaker is its conjugate base.

Charles D. Winters

The pH of this soft drink is 3.12. Soft drinks are often quite acidic.

the weaker the acid, the stronger is its conjugate base

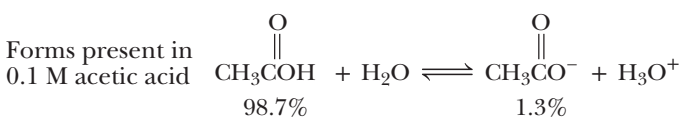
the stronger the acid, the weaker is its conjugate base

TABLE 2.2 pK_a Values for Some Organic and Inorganic Acids

	Acid	Formula	pK_a	Conjugate Base	
Weaker acid	ethane	CH_3CH_3	51	$CH_3CH_2^-$	Stronger base
	ammonia	NH_3	38	NH_2^-	
	ethanol	CH_3CH_2OH	15.9	$CH_3CH_2O^-$	
	water	H_2O	15.7	HO^-	
	methylammonium ion	$CH_3NH_3^+$	10.64	CH_3NH_2	
	bicarbonate ion	HCO_3^-	10.33	CO_3^{2-}	
	phenol	C_6H_5OH	9.95	$C_6H_5O^-$	
	ammonium ion	NH_4^+	9.24	NH_3	
	hydrogen cyanide	HCN	9.21	CN^-	
	carbonic acid	H_2CO_3	6.36	HCO_3^-	
	acetic acid	CH_3COOH	4.76	CH_3COO^-	
	benzoic acid	C_6H_5COOH	4.19	$C_6H_5COO^-$	
	phosphoric acid	H_3PO_4	2.1	$H_2PO_4^-$	
	hydronium ion	H_3O^+	−1.74	H_2O	
	sulfuric acid	H_2SO_4	−5.2	HSO_4^-	
Stronger acid	hydrogen chloride	HCl	−7	Cl^-	Weaker base
	hydrogen bromide	HBr	−8	Br^-	
	hydrogen iodide	HI	−9	I^-	

Caution: In exercises such as Example 2.2 and Problem 2.2, we ask you to select the stronger acid. You must remember that these and all other acids with ionization constants considerably less than 1.00 are *weak* acids. Thus, although acetic acid is a considerably stronger acid than water, it still is only slightly ionized in water. The ionization of acetic acid in a 0.1 M solution, for example, is only about 1.3%; the major form of this weak acid that is present in a 0.1 M solution is the unionized acid!

"stronger acid" is used as a relative term. Keep in mind that acids with K_a values less than 1 ($pK_a \geq 0$) are considered weak acids



EXAMPLE 2.2

For each value of pK_a, calculate the corresponding value of K_a. Which compound is the stronger acid?

(a) Ethanol, $pK_a = 15.9$

(b) Carbonic acid, $pK_a = 6.36$

STRATEGY

The stronger acid has the smaller value of pK_a (the larger value of K_a).

SOLUTION

(a) For ethanol, $K_a = 1.3 \times 10^{-16}$

(b) For carbonic acid, $K_a = 4.4 \times 10^{-7}$

Because the value of pK_a for carbonic acid is smaller than that for ethanol, carbonic acid is the stronger acid and ethanol is the weaker acid.

See problem 2.16

PROBLEM 2.2

For each value of K_a, calculate the corresponding value of pK_a. Which compound is the stronger acid?

(a) Acetic acid, $K_a = 1.74 \times 10^{-5}$

(b) Water, $K_a = 2.00 \times 10^{-16}$

2.4 How Do We Determine the Position of Equilibrium in an Acid–Base Reaction?

We know that HCl reacts with H_2O according to the following equilibrium:

$$HCl + H_2O \longrightarrow Cl^- + H_3O^+$$

We also know that HCl is a strong acid, which means that the position of this equilibrium lies very far to the right.

As we have seen, acetic acid reacts with H_2O according to the following equilibrium:

$$\underset{\text{Acetic acid}}{CH_3COOH} + H_2O \rightleftharpoons \underset{\text{Acetate ion}}{CH_3COO^-} + H_3O^+$$

Acetic acid is a weak acid. Only a few acetic acid molecules react with water to give acetate ions and hydronium ions, and the major species present at equilibrium in aqueous solution is CH_3COOH. The position of this equilibrium, therefore, lies very far to the left.

In the preceding two acid–base reactions, water was the base (proton acceptor). But what if we have a base other than water as the proton acceptor? How can we determine which are the major species present at equilibrium? That is, how can we determine whether the position of equilibrium lies toward the left or toward the right?

As an example, let us examine the acid–base reaction between acetic acid and ammonia to form acetate ion and ammonium ion:

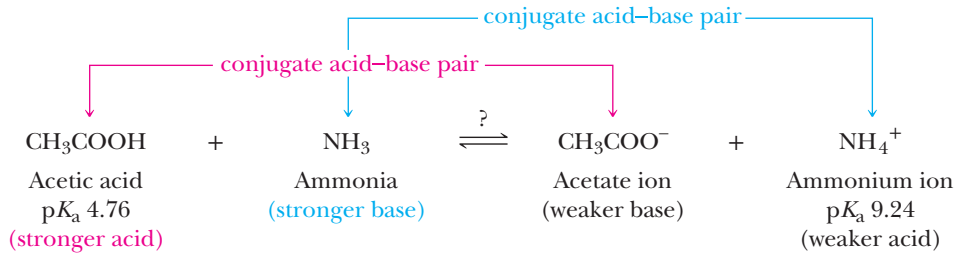
$$\underset{\substack{\text{Acetic acid}\\(\text{Acid})}}{CH_3COOH} + \underset{\substack{\text{Ammonia}\\(\text{Base})}}{NH_3} \overset{?}{\rightleftharpoons} \underset{\substack{\text{Acetate ion}\\(\text{Conjugate base}\\\text{of } CH_3COOH)}}{CH_3COO^-} + \underset{\substack{\text{Ammonium}\\\text{ion (Conjugate}\\\text{acid of } NH_3)}}{NH_4^+}$$

As indicated by the question mark over the equilibrium arrow, we want to determine whether the position of this equilibrium lies toward the left or toward the right. There are two acids present: acetic acid and ammonium ion. There are also two bases present:

Charles D. Winters

Vinegar (which contains acetic acid) and baking soda (sodium bicarbonate) react to produce sodium acetate, carbon dioxide, and water. The carbon dioxide inflates the balloon.

ammonia and acetate ion. From Table 2.2, we see that CH_3COOH (pK_a 4.76) is the stronger acid, which means that CH_3COO^- is the weaker conjugate base. Conversely, NH_4^+ (pK_a 9.24) is the weaker acid, which means that NH_3 is the stronger conjugate base. We can now label the relative strengths of each acid and base in the equilibrium:



In an acid–base reaction, the position of equilibrium always favors reaction of the stronger acid and stronger base to form the weaker acid and weaker base. Thus, at equilibrium, the major species present are the weaker acid and weaker base. In the reaction between acetic acid and ammonia, therefore, the equilibrium lies to the right, and the major species present are acetate ion and ammonium ion:

$$\underset{\text{Acetic acid (stronger acid)}}{CH_3COOH} + \underset{\text{Ammonia (stronger base)}}{NH_3} \rightleftharpoons \underset{\text{Acetate ion (weaker base)}}{CH_3COO^-} + \underset{\text{Ammonium ion (weaker acid)}}{NH_4^+}$$

HOW TO 2.2

Determine the Position of Equilibrium in an Acid–Base Reaction

1. Identify the two acids in the equilibrium; one is on the left side of the equilibrium, the other on the right side.
2. Using the information in Table 2.2, determine which acid is the stronger and which the weaker. In the absence of pK_a data, use the concepts presented in Section 2.5 to determine the stronger and weaker acid.
3. Identify the stronger base and weaker base in each equilibrium. Remember that the stronger acid gives the weaker conjugate base and the weaker acid gives the stronger conjugate base.
4. The stronger acid and stronger base react to give the weaker acid and weaker base, and the position of equilibrium lies on the side of the weaker acid and weaker base.

EXAMPLE 2.3

For each acid–base equilibrium, label the stronger acid, the stronger base, the weaker acid, and the weaker base. Then predict whether the position of equilibrium lies toward the right or toward the left.

(a) $\underset{\text{Carbonic acid}}{H_2CO_3} + OH^- \rightleftharpoons \underset{\text{Bicarbonate ion}}{HCO_3^-} + H_2O$

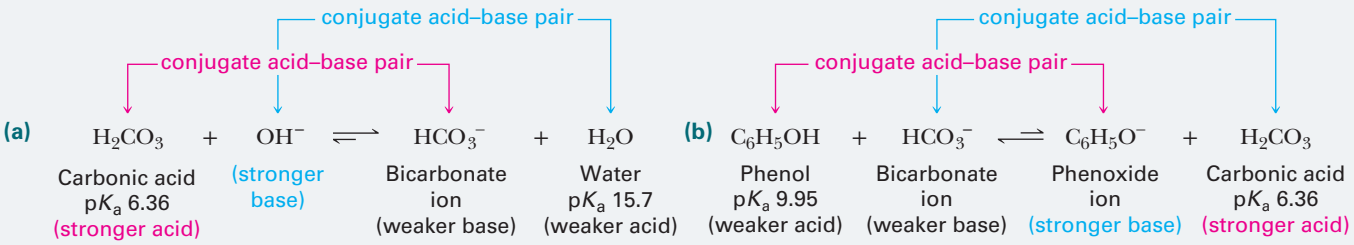
(b) $\underset{\text{Phenol}}{C_6H_5OH} + \underset{\text{Bicarbonate ion}}{HCO_3^-} \rightleftharpoons \underset{\text{Phenoxide ion}}{C_6H_5O^-} + \underset{\text{Carbonic acid}}{H_2CO_3}$

STRATEGY

Identify the two acids in the equilibrium and their relative strengths and the two bases and their relative strengths. The position of the equilibrium lies toward the weaker acid and the weaker base.

SOLUTION

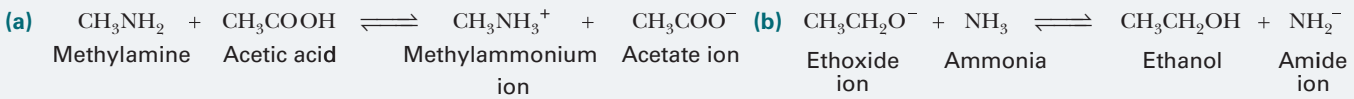
Arrows over each equilibrium show the conjugate acid–base pairs. The position of equilibrium in (a) lies toward the right. In (b) it lies toward the left.



See problems 2.11, 2.12, 2.17, 2.25

PROBLEM 2.3

For each acid–base equilibrium, label the stronger acid, the stronger base, the weaker acid, and the weaker base. Then predict whether the position of equilibrium lies toward the right or the left.



2.5 What Are the Relationships between Acidity and Molecular Structure?

Now let us examine the relationship between the acidity of organic compounds and their molecular structure. The most important factor in determining the relative acidities of organic acids is the relative stability of the anion, A^-, formed when the acid, HA, transfers a proton to a base. We can understand the relationship involved by considering (A) the electronegativity of the atom bonded to H, (B) resonance, (C) the inductive effect, and (D) the size and delocalization of charge on A^-. We will look at each of these factors briefly in this chapter. We will study them more fully in later chapters when we deal with particular functional groups.

A. Electronegativity: Acidity of HA within a Period of the Periodic Table

Recall that electronegativity is a measure of an atom's attraction for electrons it shares in a covalent bond with another atom. The more electronegative an atom is, the greater its ability to sustain electron density around itself. The relative acidity of the hydrogen acids within a period of the Periodic Table is determined by the stability of A^-, that is, by the stability of the anion that forms when a proton is transferred from HA to a base. Thus, the greater the electronegativity of A, the greater the stability of the anion A^-, and the stronger the acid HA. For example, carbon and oxygen are in the same period of the Periodic Table. Because oxygen is more electronegative than carbon, oxygen is better able to sustain the added electron density incurred when it is negatively charged than is carbon when it is negatively charged.

when comparing negatively charged *atoms in the same period* of the Periodic Table, **the more electronegative the atom, the better it is at sustaining the negative charge**

	$H_3C—H$	$H_2N—H$	HO—H	F—H
pK_a	51	38	15.7	3.5
Electronegativity of A in A—H	2.5	3.0	3.5	4.0

Increasing acid strength

Caution: Electronegativity is the major factor when comparing the stability of negatively charged atoms in the same period of the Periodic Table. Other factors, which we will discuss in Section 2.5D and in future chapters, will become significant when comparing atoms in the same group (vertical column) of the Periodic Table.

B. Resonance Effect: Delocalization of the Charge in A^-

Carboxylic acids are weak acids: Values of pK_a for most unsubstituted carboxylic acids fall within the range from 4 to 5. The value of pK_a for acetic acid, for example, is 4.76:

$$\underset{\text{A carboxylic acid}}{CH_3COOH} + H_2O \rightleftharpoons \underset{\text{A carboxylate anion}}{CH_3COO^-} + H_3O^+ \quad pK_a = 4.76$$

Values of pK_a for most alcohols, compounds that also contain an —OH group, fall within the range from 15 to 18; the value of pK_a for ethanol, for example, is 15.9:

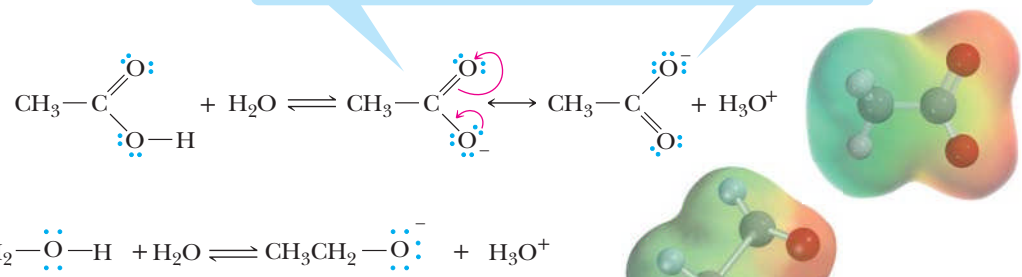
$$\underset{\text{An alcohol}}{CH_3CH_2O—H} + H_2O \rightleftharpoons \underset{\text{An alkoxide ion}}{CH_3CH_2O^-} + H_3O^+ \quad pK_a = 15.9$$

Thus, alcohols are slightly weaker acids than water $(pK_a = 15.7)$ and are much weaker acids than carboxylic acids.

We account for the greater acidity of carboxylic acids compared with alcohols in part by using the resonance model and looking at the relative stabilities of the alkoxide ion and the carboxylate ion. Our guideline is this: *The more stable the anion, the farther the position of equilibrium is shifted toward the right and the more acidic is the compound.*

There is no resonance stabilization in an alkoxide anion. The ionization of a carboxylic acid, however, gives an anion for which we can write two equivalent contributing structures in which the negative charge of the anion is delocalized; that is, it is spread evenly over the two oxygen atoms:

these contributing structures are equivalent; the carboxylate anion is stabilized by delocalization of the negative charge across the two oxygen atoms



the alkoxide ion has no resonance contributing structures. Its negative charge is localized on the sole oxygen atom

Because of the delocalization of its charge, a carboxylate anion is significantly more stable than an alkoxide anion. Therefore, the equilibrium for the ionization of a carboxylic acid

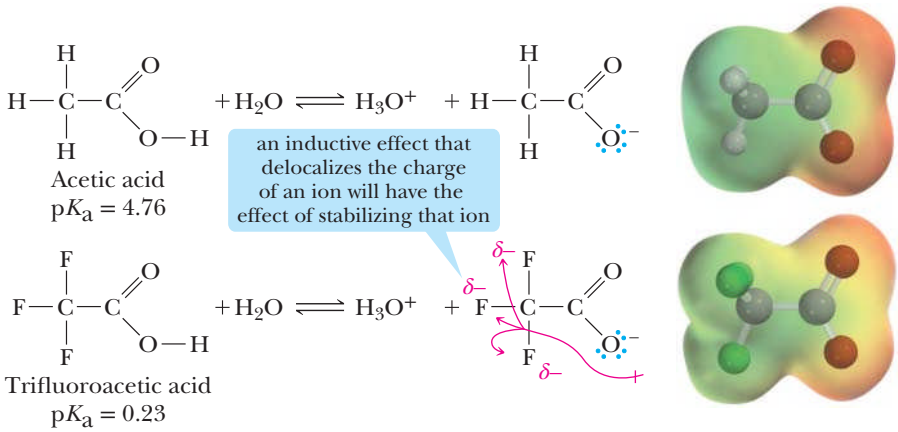
a resonance effect that delocalizes the charge of an ion will have the effect of stabilizing that ion

is shifted to the right relative to that for the ionization of an alcohol, and a carboxylic acid is a stronger acid than an alcohol.

C. The Inductive Effect: Withdrawal of Electron Density from the HA Bond

Inductive effect The polarization of electron density transmitted through covalent bonds caused by a nearby atom of higher electronegativity.

The **inductive effect** is the polarization of electron density transmitted through covalent bonds by a nearby atom of higher electronegativity. We see the operation of the inductive effect when we compare the acidities of acetic acid (pK_a 4.76) and trifluoroacetic acid (pK_a 0.23). Fluorine is more electronegative than carbon and polarizes the electrons of the C—F bond, creating a partial positive charge on the carbon of the $—CF_3$ group. The partial positive charge, in turn, withdraws electron density from the negatively charged $—CO_2^-$ group. The withdrawal of electron density delocalizes the negative charge and makes the conjugate base of trifluoroacetic acid more stable than the conjugate base of acetic acid. The delocalizing effect is apparent when the electron density map of each conjugate base is compared.



Notice that the oxygen atoms on the trifluoroacetate ion are less negative (represented by a lighter shade of red). Thus, the equilibrium for ionization of trifluoroacetic acid is shifted more to the right relative to the ionization of acetic acid, making trifluoroacetic acid more acidic than acetic acid.

D. Size and the Delocalization of Charge in A^-

An important principle in determining the relative stability of unionized acids, HA, is the stability of the conjugate base anion, A^-, resulting from the loss of a proton. The more stable the anion, the greater the acidity of the acid. For example, the relative acidity of the hydrogen halides, HX, is related to the size of the atom bearing the negative charge. The principles of physics teach us that a system bearing a charge (either negative or positive) is more stable if the charge is delocalized. The larger the volume over which the charge of an anion (or cation) is delocalized, the greater the stability of the anion.

Recall from general chemistry that atomic size is a periodic property.

when comparing negatively charged *atoms in the same group* of the Periodic Table, **the larger the atom bearing the negative charge, the better it is at sustaining the charge**

1. For main group elements, atomic radii increase significantly going down a group in the Periodic Table. From the top to the bottom of a group in the Periodic Table, the atomic radii increase because electrons occupy orbitals that are successively larger as the value of *n*, the principal quantum number, increases. Thus, for the halogens (Group 8A elements), iodine has the largest atomic radius and fluorine has the smallest (I > Br > Cl > F).

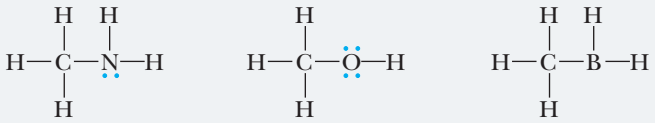
2. Anions are always larger than the atoms from which they are derived. For anions, the nuclear charge is unchanged, but the added electron(s) introduce new repulsions and electron clouds swell. Among the halide ions, I^- has the largest atomic radius and F^- has the smallest ($I^- > Br^- > Cl^- > F^-$).

Thus, when considering the relative acidities of the hydrogen halide acids, we need to consider the relative stabilities of the resulting halide ions formed by ionization of the acid. We know that HI is the strongest acid and that HF is the weakest. We account for this trend

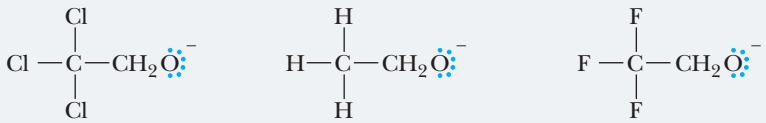
by the fact that the negative charge on iodide ion is delocalized over a larger area than is the negative charge on bromide ion. The negative charge on bromide ion in turn is delocalized over a larger area than is the negative charge on chloride ion, and so forth. Thus, HI is the strongest acid in the series because iodide ion is the most stable anion, and HF is the weakest acid because fluoride ion is the least stable ion.

EXAMPLE 2.4

(a) Arrange the following compounds in the order from most acidic to least acidic.



(b) Arrange the following compounds in order from most basic to least basic.



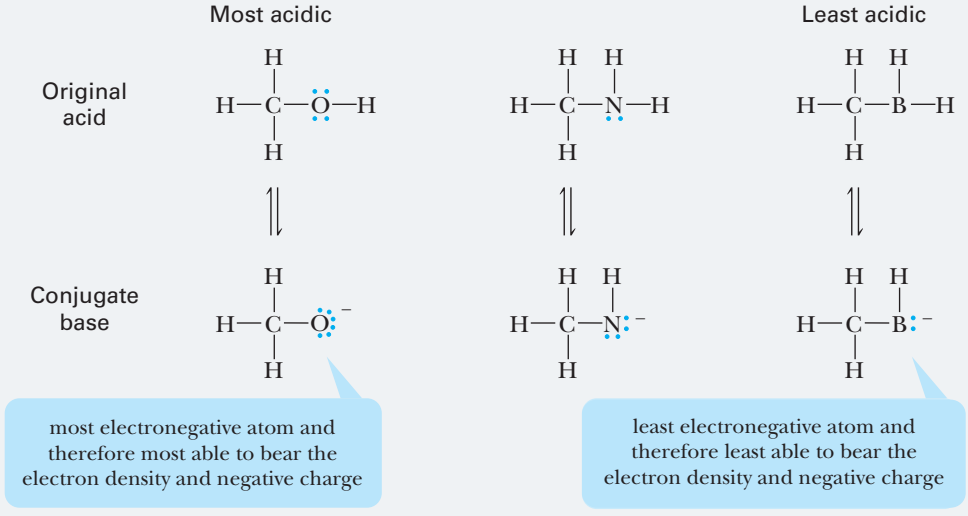
STRATEGY

When determining acidity, assess the stability of the conjugate base—the compound formed after the acid has transferred its proton to a base. Any feature (e.g., electronegativity, resonance, inductive effect, or anion size) that helps to stabilize the conjugate base will make the original acid more acidic. When determining the basicity of a negatively charged species, assess the stability of the base. Any feature (e.g., electronegativity, resonance, or inductive effect) that helps to stabilize the base will make it less basic. That is, a more stable base will be less reactive.

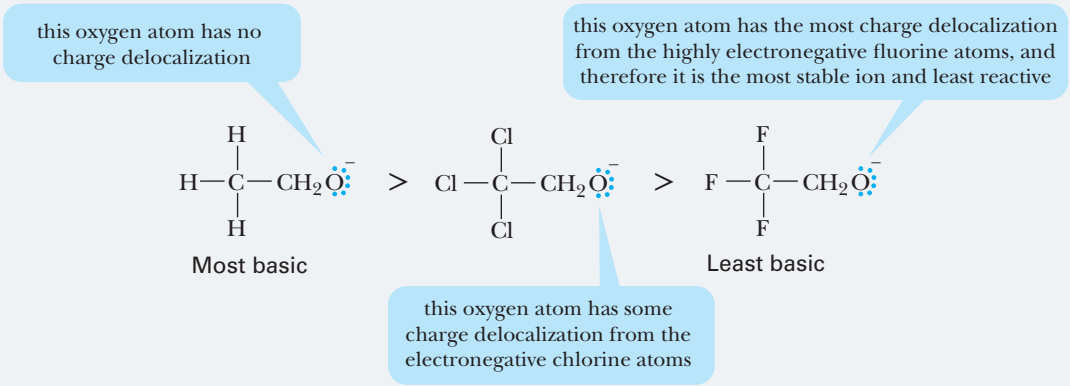
SOLUTION

Because the elements compared in this example (B, C, and O) are all in the same period of the Periodic Table, the stability of the conjugate bases can be compared based on the electronegativity of the element bearing the negative charge. Oxygen, the most electronegative element, is most able to bear the electron density and negative charge. Boron, the least electronegative element, is least able to bear the electron density and negative charge.

(a)



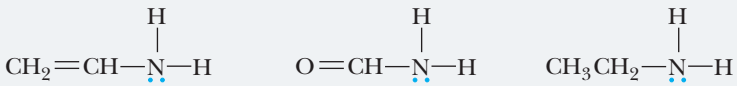
(b) The stability of bases can be compared based on the extent of an inductive effect within each compound. Fluorine, the most electronegative element, will exert a strong inductive effect on the negatively charged oxygen, thereby delocalizing the negative charge to some extent. This delocalization of negative charge makes the $F_3CCH_2O^-$ ion more stable than either of the other two. Chlorine can also exert an inductive effect on the negatively charged oxygen. Chlorine, however, is less electronegative than fluorine, so the stabilizing effect is less.



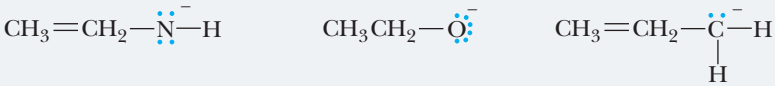
See problems 2.20–2.22

PROBLEM 2.4

(a) Arrange the following compounds in the order from most acidic to least acidic.



(b) Arrange the following compounds in the order from most basic to least basic.

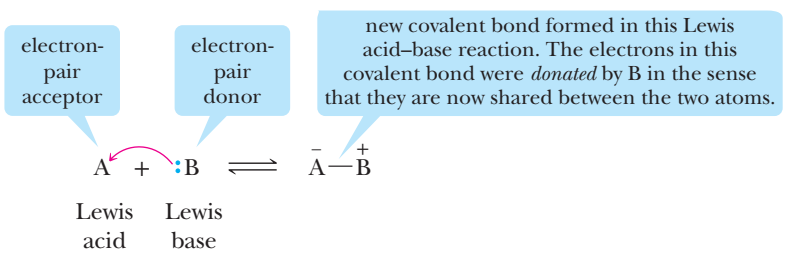


2.6 What Are Lewis Acids and Bases?

Lewis acid Any molecule or ion that can form a new covalent bond by accepting a pair of electrons.

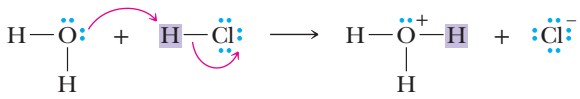
Lewis base Any molecule or ion that can form a new covalent bond by donating a pair of electrons.

Gilbert Lewis, who proposed that covalent bonds are formed by the sharing of one or more pairs of electrons (Section 1.2), further expanded the theory of acids and bases to include a group of substances not included in the Brønsted–Lowry concept. According to the Lewis definition, an **acid** is a species that can form a new covalent bond by accepting a pair of electrons; a **base** is a species that can form a new covalent bond by donating a pair of electrons. In the following general equation, the Lewis acid, A, accepts a pair of electrons in forming the new covalent bond and acquires a negative formal charge, while the Lewis base, :B, donates the pair of electrons in forming the new covalent bond and acquires a positive formal charge:



Note that, although we speak of a Lewis base as "donating" a pair of electrons, the term is not fully accurate. "Donating" in this case does not imply that the electron pair under consideration is removed completely from the valence shell of the base. Rather, "donating" means that the electron pair is shared with another atom to form a covalent bond.

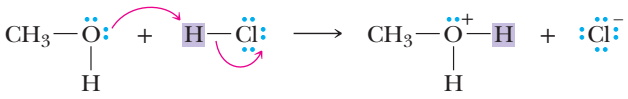
As we will see in the chapters that follow, a great many organic reactions can be interpreted as Lewis acid–base reactions. Perhaps the most important (but not the only) Lewis acid is the proton. Isolated protons, of course, do not exist in solution; rather, a proton attaches itself to the strongest available Lewis base. When HCl is dissolved in water, for example, the strongest available Lewis base is an H_2O molecule, and the following proton-transfer reaction takes place:



Hydronium ion

When HCl is dissolved in methanol, the strongest available Lewis base is a CH_3OH molecule, and the following proton-transfer reaction takes place. An **oxonium ion** is an ion that contains an oxygen atom with three bonds and bears a positive charge.

Oxonium ion An ion that contains an oxygen atom bonded to three other atoms or groups of atoms and bears a positive charge.



Methanol (a Lewis base) An oxonium ion

Table 2.3 gives examples of the most important types of Lewis bases we will encounter in this text arranged in order of their increasing strength in proton-transfer reactions. Note that each of the Lewis bases has at least one atom with an unshared pair of electrons. It is this atom that functions as the Lewis base. Ethers are organic derivatives of water in which both hydrogens of water are replaced by carbon groups. We study the properties of ethers along with those of alcohols in Chapter 8. We study the properties of amines in Chapter 10.

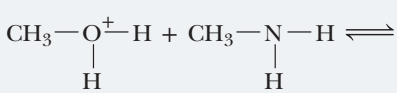
TABLE 2.3 Some Organic Lewis Bases and Their Relative Base Strengths in Proton-Transfer Reactions

Halide Ions	Water, Alcohols, and Ethers	Ammonia and Amines	Hydroxide Ion and Alkoxide Ions	Amide Ions
$:\ddot{Cl}:^-$	$H-\ddot{O}-H$	$H-\ddot{N}(H)-H$	$H-\ddot{O}:^-$	$H-\ddot{N}:^-(H)$
$:\ddot{Br}:^-$	$CH_3-\ddot{O}-H$	$CH_3-\ddot{N}(H)-H$	$CH_3-\ddot{O}:^-$	$CH_3-\ddot{N}:^-(H)$
$:\ddot{I}:^-$	$CH_3-\ddot{O}-CH_3$	$CH_3-\ddot{N}(CH_3)-H$		$CH_3-\ddot{N}:^-(CH_3)$
		$CH_3-\ddot{N}(CH_3)-CH_3$		

Very weak → Weak → Strong → Stronger → Very strong

EXAMPLE 2.5

Complete this acid–base reaction. Use curved arrows to show the redistribution of electrons in the reaction. In addition, predict whether the position of this equilibrium lies toward the left or the right.

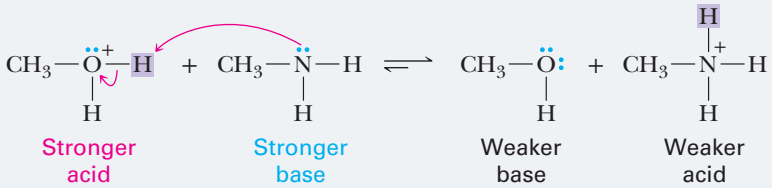


STRATEGY

First, add unshared pairs of electrons on the reacting atoms to give each a complete octet. Then identify the Lewis base (the electron-pair donor) and the Lewis acid (the electron-pair acceptor). The position of equilibrium lies on the side of the weaker acid and weaker base.

SOLUTION

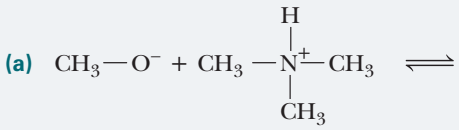
Proton transfer takes place to form an alcohol and an ammonium ion. We know from Table 2.3 that amines are stronger bases than alcohols. We also know that the weaker the base, the stronger its conjugate acid, and vice versa. From this analysis, we conclude that the position of this equilibrium lies to the right, on the side of the weaker acid and the weaker base.



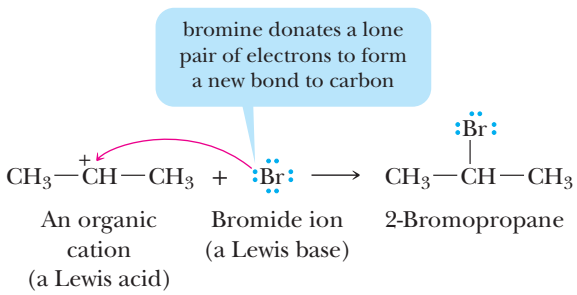
See problems 2.7, 2.8, 2.11, 2.26–2.32

PROBLEM 2.5

Complete this acid–base reaction. First add unshared pairs of electrons on the reacting atoms to give each atom a complete octet. Use curved arrows to show the redistribution of electrons in the reaction. In addition, predict whether the position of the equilibrium lies toward the left or the right.



Another type of Lewis acid we will encounter in later chapters is an organic cation in which a carbon is bonded to only three atoms and bears a positive formal charge. Such carbon cations are called carbocations. Consider the reaction that occurs when the following organic cation reacts with a bromide ion:



In this reaction, the organic cation is the electron-pair acceptor (the Lewis acid), and bromide ion is the electron-pair donor (the Lewis base).

EXAMPLE 2.6

Complete the following Lewis acid–base reaction. Show all electron pairs on the reacting atoms and use curved arrows to show the flow of electrons in the reaction:

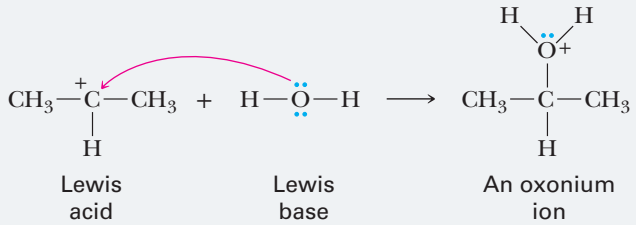
$$CH_3-\overset{+}{C}H-CH_3 + H_2O \longrightarrow$$

STRATEGY

Determine which compound will be the electron-pair donor and which will be the electron-pair acceptor. *Hint:* Compounds with empty orbitals in their valence shell usually act as Lewis acids.

SOLUTION

The trivalent carbon atom in the organic cation has an empty orbital in its valence shell and, therefore, is the Lewis acid. Water is the Lewis base.



See problems 2.30–2.32

PROBLEM 2.6

Write an equation for the reaction between each Lewis acid–base pair, showing electron flow by means of curved arrows. (*Hint:* Aluminum is in Group 3A of the Periodic Table, just under boron. Aluminum in $AlCl_3$ has only six electrons in its valence shell and thus has an incomplete octet.)

(a) $Cl^- + AlCl_3 \longrightarrow$ **(b)** $CH_3Cl + AlCl_3 \longrightarrow$

SUMMARY OF KEY QUESTIONS

2.1 What Are Arrhenius Acids and Bases?

- An **Arrhenius acid** is a substance that dissolves in aqueous solution to produce H_3O^+ ions.
- An **Arrhenius base** is a substance that dissolves in aqueous solution to produce OH^- ions.

2.2 What Are Brønsted–Lowry Acids and Bases?

- A **Brønsted–Lowry acid** is a proton donor.
- A **Brønsted–Lowry base** is a proton acceptor.
- Neutralization of an acid by a base is a **proton-transfer reaction** in which the acid is transformed into its **conjugate base**, and the base is transformed into its **conjugate acid**.

2.3 How Do We Measure the Strength of an Acid or Base?

- A **strong acid** or **strong base** is one that completely ionizes in water.
- A **weak acid** or **weak base** is one that only partially ionizes in water.
- The strength of a weak acid is expressed by its **ionization constant, K_a**.
- The larger the value of K_a, the stronger the acid, $pK_a = -\log K_a$.

2.4 How Do We Determine the Position of Equilibrium in an Acid–Base Reaction?

- In an acid–base reaction, the **position of equilibrium** favors the reaction of the stronger acid and the stronger base to form the weaker acid and the weaker base.

2.5 What Are the Relationships between Acidity and Molecular Structure?

The relative acidities of the organic acids, HA, are determined by

- the electronegativity of A.
- the **resonance stabilization** of the conjugate base, A^-.
- the electron-withdrawing **inductive effect**, which also stabilizes the conjugate base.
- the size of the atom with the negative charge on the conjugate base.

2.6 What Are Lewis Acids and Bases?

- A **Lewis acid** is a species that forms a new covalent bond by accepting a pair of electrons (an electron-pair acceptor).
- A **Lewis base** is a species that forms a new covalent bond by donating a pair of electrons (an electron-pair donor).

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. If NH_3 were to behave as an acid, its conjugate base would be NH_2^-. (2.2)

2. Delocalization of electron density is a stabilizing factor. (2.5)

3. Amide ion, NH_2^-, is a Lewis base. (2.6)

4. H_3O^+ is a stronger acid than NH_4^+ and, therefore, NH_3 is a stronger base than H_2O. (2.3)

5. Inductive effects can be used to describe electron delocalization. (2.5)

6. The direction of equilibrium in an acid–base reaction favors the side containing the stronger acid and stronger base. (2.4)

7. The conjugate base of CH_3CH_2OH is $CH_3CH_2O^-$. (2.2)

8. CH_3^+ and NH_4^+ are Lewis acids. (2.6)

9. When an acid, HA, dissolves in water, the solution becomes acidic because of the presence of H^+ ions. (2.1)

10. Between a strong acid and a weak acid, the weak acid will give rise to the stronger conjugate base. (2.4)

11. H_2O can function as an acid (proton donor) and as a base (proton acceptor). (2.2)

12. The strongest base that can exist in aqueous solution is OH^-. (2.4)

13. A strong acid is one that completely ionizes in aqueous solution. (2.3)

14. NH_3 is a Lewis base. (2.6)

15. A Brønsted–Lowry acid is a proton donor. (2.2)

16. When comparing the relative strength of acids, the stronger acid has the smaller value of pK_a. (2.3)

17. When comparing the relative strengths of acids, the stronger acid has the smaller value of K_a. (2.3)

18. The formulas of a conjugate acid–base pair differ only by a proton. (2.2)

19. A Lewis base is an electron pair donor. (2.6)

20. Acetic acid, CH_3COOH, is a stronger acid than carbonic acid, H_2CO_3, and, therefore, acetate ion, CH_3COO^-, is a stronger base than bicarbonate ion, HCO_3^-. (2.2)

21. The strongest acid that can exist in aqueous solution is H_3O^+. (2.4)

22. A Lewis acid–base reaction results in the formation of a new covalent bond between the Lewis acid and the Lewis base. (2.6)

23. When a base accepts a proton in an acid–base reaction, it is converted into its conjugate base. (2.2)

24. When a metal hydroxide, MOH, dissolves in water, the solution becomes basic because of the presence of hydroxide ions, OH^-. (2.1)

25. A Lewis acid is a proton acceptor. (2.6)

26. If NH_3 were to behave as a base, its conjugate acid would be NH_4^+. (2.2)

27. Resonance effects can be used to describe electron delocalization. (2.5)

28. All Lewis acid–base reactions involve transfer of a proton from the acid to the base.

29. BF_3 is a Lewis acid. (2.6)

30. When HCl dissolves in water, the major ions present are H^+ and Cl^-. (2.3)

31. According to the Arrhenius definitions, acids and bases are limited substances that dissolve in water. (2.1)

32. Acid–base reactions take place only in aqueous solution. (2.6)

33. The conjugate acid of HCO_3^- is H_2CO_3. (2.2)

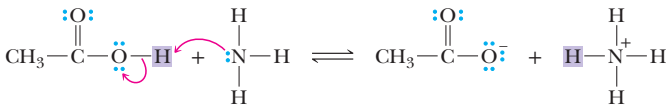
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) T (3) T (4) T (5) T (6) F (7) T (8) F (9) F
(10) T (11) T (12) T (13) T (14) T (15) T (16) T (17) F (18) T
(19) T (20) F (21) T (22) T (23) F (24) T (25) F (26) T (27) T
(28) F (29) T (30) F (31) T (32) F (33) T

KEY REACTIONS

1. Proton-Transfer Reaction (Section 2.2)

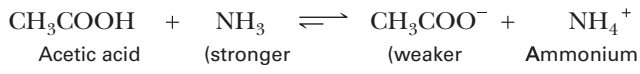
This reaction involves the transfer of a proton from a proton donor (a Brønsted–Lowry acid) to a proton acceptor (a Brønsted–Lowry base):



Acetic acid (proton donor) Ammonia (proton acceptor) Acetate ion Ammonium ion

2. Position of Equilibrium in an Acid–Base Reaction (Section 2.4)

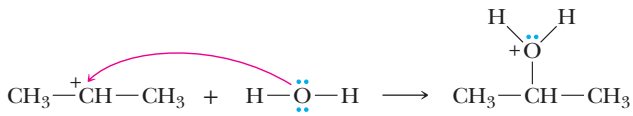
Equilibrium favors reaction of the stronger acid with the stronger base to give the weaker acid and the weaker base:



Acetic acid pK_a 4.76 (stronger acid) | (stronger base) | (weaker base) | Ammonium ion pK_a 9.24 (weaker acid)

3. Lewis Acid–Base Reaction (Section 2.6)

A Lewis acid–base reaction involves sharing an electron pair between an electron-pair donor (a Lewis base) and an electron-pair acceptor (a Lewis acid):



A Lewis acid A Lewis base An oxonium ion

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 2.1 Arrhenius Acids and Bases

2.7 Complete the net ionic equation for each acid placed in water. Use curved arrows to show the flow of electron pairs in each reaction. Also, for each reaction, determine the direction of equilibrium, using Table 2.2 as a reference for the pK_a values of proton acids. **(See Examples 2.1, 2.5)**

(a) $NH_4^+ + H_2O \rightleftharpoons$ (c) $CH_3-\overset{\overset{O}{\|}}{C}-OH + H_2O \rightleftharpoons$

(b) $HCO_3^- + H_2O \rightleftharpoons$ (d) $CH_3CH_2O^- + H_2O \rightleftharpoons$

2.8 Complete the net ionic equation for each base placed in water. Use curved arrows to show the flow of electron pairs in each reaction. Also, for each reaction, determine the direction of equilibrium, using Table 2.2 as a reference for the pK_a values of proton acids formed. **(See Examples 2.1, 2.5)**

(a) $CH_3NH_2 + H_2O \rightleftharpoons$ (d) $CO_3^{2-} + H_2O \rightleftharpoons$

(b) $HSO_4^- + H_2O \rightleftharpoons$ (e) $CN^- + H_2O \rightleftharpoons$

(c) $Br^- + H_2O \rightleftharpoons$

SECTION 2.2 Brønsted–Lowry Acids and Bases

2.9 How are the formulas of the members of a conjugate acid–base pair related to each other? Within a pair, how can you tell which is the acid?

2.10 Write the structural formula for the conjugate acids of the following structures.

(a) $CH_3-CH_2-\overset{\overset{H}{|}}{N}-H$ (d) $CH_2=\ddot{N}-CH_3$

(b) CH_3CH_2SH (e) $CH_3CH_2\ddot{C}H_2$

(c) $H-\overset{\overset{H}{|}}{N}-CH_2-CH_2-\ddot{O}H$ (f) CH_3OCH_3

2.11 Complete a net ionic equation for each proton-transfer reaction, using curved arrows to show the flow of electron pairs in each reaction. In addition, write Lewis structures for all starting materials and products. Label the original acid and its conjugate base; label the original base and its conjugate acid. If you are uncertain about which substance in each equation is the proton donor, refer to Table 2.2 for the pK_a values of proton acids. **(See Examples 2.3, 2.5)**

(a) $NH_3 + HCl \longrightarrow$ (e) $NH_4^+ + OH^- \longrightarrow$

(b) $CH_3CH_2O^- + HCl \longrightarrow$ (f) $CH_3COO^- + CH_3NH_3^+ \longrightarrow$

(c) $HCO_3^- + OH^- \longrightarrow$ (g) $CH_3CH_2O^- + NH_4^+ \longrightarrow$

(d) $CH_3COO^- + NH_4^+ \longrightarrow$ (h) $CH_3NH_3^+ + OH^- \longrightarrow$

***2.12** One kind of baking powder contains sodium bicarbonate and calcium dihydrogen phosphate: When water is added, the following reaction occurs. **(See Example 2.3)**

$$HCO_3^-(aq) + H_2PO_4^-(aq) \longrightarrow H_2CO_3(aq) + HPO_4^{2-}(aq)$$

Identify the two acids and the two bases in this reaction. (The H_2CO_3 decomposes to release CO_2, which causes the cake to rise.)

2.13 Each of these molecules and ions can function as a base. Complete the Lewis structure of each base, and write the structural formula of the conjugate acid formed by its reaction with HCl.

(a) CH_3CH_2OH (c) $HC\equiv C^-$ (e) HCO_3^-

(b) $\overset{\overset{O}{\|}}{H}CH$ (d) $(CH_3)_2NH$ (f) N_3^-

2.14 Offer an explanation for the following observations:

(a) H_3O^+ is a stronger acid than NH_4^+.

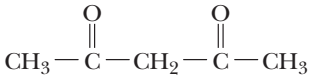
(b) Nitric acid, HNO_3, is a stronger acid than nitrous acid, HNO_2 (pK_a 3.7).

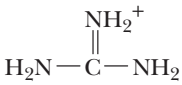
(c) Ethanol, CH_3CH_2OH, and water have approximately the same acidity.

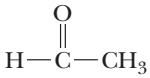
(d) Trichloroacetic acid, CCl_3COOH (pK_a 0.64), is a stronger acid than acetic acid, CH_3COOH (pK_a 4.74).

(e) Trifluoroacetic acid, CF_3COOH (pK_a 0.23), is a stronger acid than trichloroacetic acid, CCl_3COOH (pK_a 0.64).

2.15 Select the most acidic proton in the following compounds:

(a) 

(b) 

(c) 

SECTION 2.3 Quantitative Measure of Acid Strength

2.16 Which has the larger numerical value? **(See Example 2.2)**

(a) The pK_a of a strong acid or the pK_a of a weak acid?

(b) The K_a of a strong acid or the K_a of a weak acid?

***2.17** In each pair, select the stronger acid: **(See Example 2.3)**

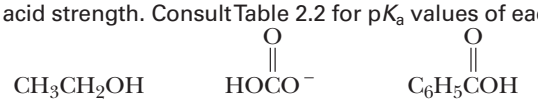
(a) Pyruvic acid (pK_a 2.49) or lactic acid (pK_a 3.85)

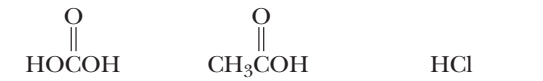
(b) Citric acid (pK_{a1} 3.08) or phosphoric acid (pK_{a1} 2.10)

(c) Nicotinic acid (niacin, K_a 1.4×10^{-5}) or acetylsalicylic acid (aspirin, K_a 3.3×10^{-4})

(d) Phenol (K_a 1.12×10^{-10}) or acetic acid (K_a 1.74×10^{-5})

2.18 Arrange the compounds in each set in order of increasing acid strength. Consult Table 2.2 for pK_a values of each acid.

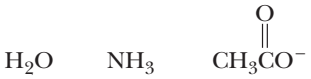
(a) 
Ethanol Bicarbonate ion Benzoic acid

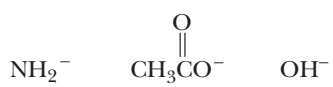
(b) 
Carbonic acid Acetic acid Hydrogen chloride

2.19 Arrange the compounds in each set in order of increasing base strength. Consult Table 2.2 for pK_a values of the conjugate acid of each base. (*Hint:* The stronger the acid, the weaker is its conjugate base, and vice versa.)

(a) 

(b) 

(c) 

(d) 

2.20 Using only the Periodic Table, choose the stronger acid of each pair. **(See Example 2.4)**

(a) H_2Se or HBr

(b) H_2Se or H_2Te

(c) CH_3OH or CH_3SH

(d) HCl or HBr

2.21 Explain why H_2S is a stronger acid than H_2O. **(See Example 2.4)**

2.22 Which is the stronger Brønsted–Lowry base, $CH_3CH_2O^-$ or $CH_3CH_2S^-$? What is the basis for your selection? **(See Example 2.4)**

SECTION 2.4 Position of Equilibrium in Acid–Base Reactions

2.23 Unless under pressure, carbonic acid in aqueous solution breaks down into carbon dioxide and water, and carbon dioxide is evolved as bubbles of gas. Write an equation for the conversion of carbonic acid to carbon dioxide and water.

2.24 For each of the following compounds, will carbon dioxide be evolved when sodium bicarbonate is added to an aqueous solution of the compound?

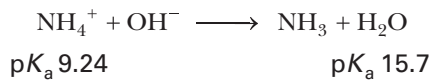
(a) H_2SO_4 (b) CH_3CH_2OH (c) NH_4Cl

2.25 Acetic acid, CH_3COOH, is a weak organic acid, pK_a 4.76. Write equations for the equilibrium reactions of acetic acid with each base. Which equilibria lie considerably toward the left? Which lie considerably toward the right? **(See Example 2.3)**

(a) $NaHCO_3$ (b) NH_3 (c) H_2O (d) NaOH

2.26 The amide ion, NH_2^-, is a very strong base; it is even stronger than OH^-. Write an equation for the reaction that occurs when amide ion is placed in water. Use this equation to show why the amide ion cannot exist in aqueous solution. **(See Example 2.5)**

2.27 For an acid–base reaction, one way to indicate the predominant species at equilibrium is to say that the reaction arrow points to the acid with the higher value of pK_a. For example **(See Example 2.5)**



Explain why this rule works.

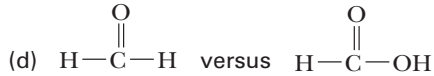
SECTION 2.5 Relationship between Acidity and Basicity and Molecular Structure

2.28 For each pair of compounds, determine the stronger acid without using Table 2.2 and provide a rationale for your answer choice. **(See Example 2.5)**

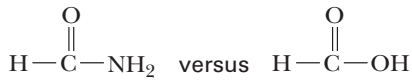
(a) $CF_3CH_2CH_2OH$ versus $CBr_3CH_2CH_2OH$

(b) $H_2C{=}CHOH$ versus CH_3CH_2OH

(c) HBr versus HCl

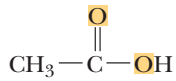
(d) 

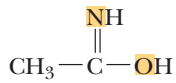
(e) CH_3CH_2OH versus CH_3SCH_2OH

(f)  versus

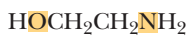
(g) CH_3NH_2 versus FCH_2NH_2

2.29 For each compound, determine the more basic of the atoms highlighted in yellow and provide a rationale for your answer. **(See Example 2.5)**

(a) 

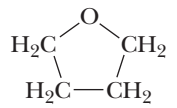
(b) 

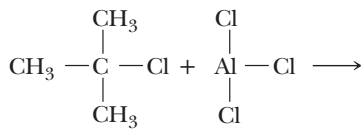
(c) 

(d) 

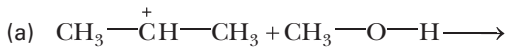
SECTION 2.6 Lewis Acids and Bases

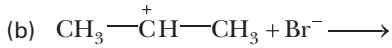
2.30 Complete the following acid–base reactions, using curved arrow notation to show the flow of electron pairs. In solving these problems, it is essential that you show all valence electrons for the atoms participating directly in each reaction. **(See Examples 2.5, 2.6)**

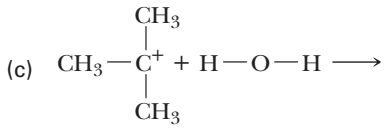
(a) BF_3 +  ⟶

(b) 

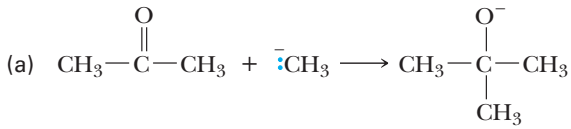
2.31 Complete equations for these reactions between Lewis acid–Lewis base pairs. Label which starting material is the Lewis acid and which is the Lewis base, and use a curved arrow to show the flow of the electron pair in each reaction. In solving these problems, it is essential that you show all valence electrons for the atoms participating directly in each reaction. **(See Examples 2.5, 2.6)**

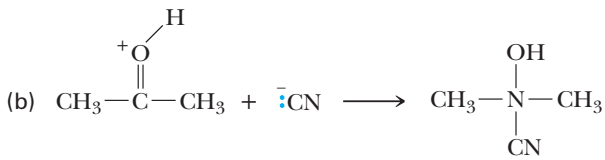
(a) 

(b) 

(c) 

2.32 Use curved arrow notation to show the flow of electron pairs in each Lewis acid–base reaction. Be certain to show all valence electron pairs on each atom participating in the reaction. **(See Examples 2.5, 2.6)**

(a) 

(b) 

(c) $CH_3O^- + CH_3—Br \longrightarrow CH_3—O—CH_3 + Br^-$

LOOKING AHEAD

2.33 Alcohols (Chapter 8) are weak organic acids, pK_a 15–18. The pK_a of ethanol, CH_3CH_2OH, is 15.9. Write equations for the equilibrium reactions of ethanol with each base. Which equilibria lie considerably toward the right? Which lie considerably toward the left?

(a) $NaHCO_3$ (b) NaOH (c) $NaNH_2$ (d) NH_3

2.34 Phenols (Chapter 9) are weak acids, and most are insoluble in water. Phenol, C_6H_5OH (pK_a 9.95), for example, is only slightly soluble in water, but its sodium salt, $C_6H_5O^-Na^+$, is quite soluble in water. In which of these solutions will phenol dissolve?

(a) Aqueous NaOH (c) Aqueous Na_2CO_3

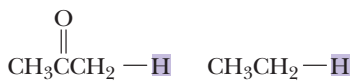
(b) Aqueous $NaHCO_3$

2.35 Carboxylic acids (Chapter 13) of six or more carbons are insoluble in water, but their sodium salts are very soluble in water. Benzoic acid, C_6H_5COOH (pK_a 4.19), for example, is insoluble in water, but its sodium salt, $C_6H_5COO^-Na^+$, is quite soluble in water. In which of these solutions will benzoic acid dissolve?

(a) Aqueous NaOH (c) Aqueous Na_2CO_3

(b) Aqueous $NaHCO_3$ (d) Aqueous $NaCH_3CO_2$

2.36 As we shall see in Chapter 15, hydrogens on a carbon adjacent to a carbonyl group are far more acidic than those not adjacent to a carbonyl group. The highlighted H in propanone, for example, is more acidic than the highlighted H in ethane:



Propanone pK_a = 22 Ethane pK_a = 51

Account for the greater acidity of propanone in terms of

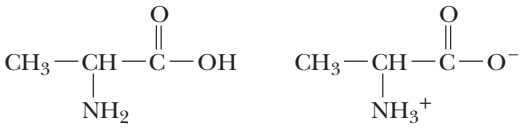
(a) the inductive effect and

(b) the resonance effect.

2.37 Explain why the protons in dimethyl ether, $CH_3—O—CH_3$, are not very acidic.

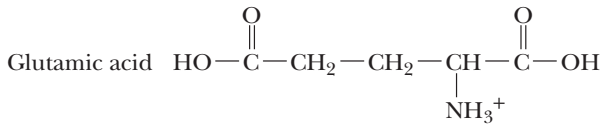
2.38 Predict whether sodium hydride, NaH, will act as a base or an acid, and provide a rationale for your decision.

***2.39** Alanine is one of the 20 amino acids (it contains both an amino and a carboxyl group) found in proteins (Chapter 18). Is alanine better represented by the structural formula A or B? Explain.



A B

***2.40** Glutamic acid is another of the amino acids found in proteins (Chapter 18):



Glutamic acid has two carboxyl groups, one with pK_a 2.10, the other with pK_a 4.07.

(a) Which carboxyl group has which pK_a?

(b) Account for the fact that one carboxyl group is a considerably stronger acid than the other.

GROUP LEARNING ACTIVITIES

2.41 Take turns naming one of the functional groups presented in Section 1.7. Discuss and show how each functional group can act as an acid, a base, or both.

2.42 Starting at the top of the following table, take turns explaining why each acid is less acidic than the acid directly below it. Which factor in Section 2.5 plays the most dominant role in your explanation?

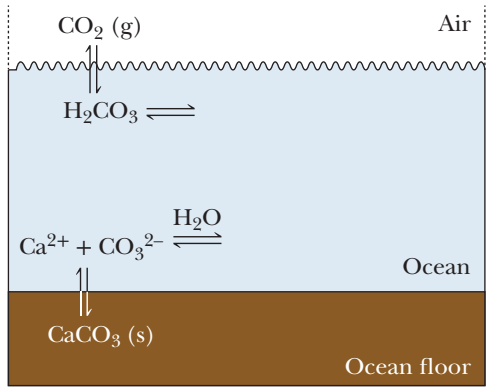
pK_a Values for Representative Acids

Acid	Formula	pK_a
ethane	CH_3CH_3	51
ammonia	NH_3	38
ethanol	CH_3CH_2OH	15.9
ethanethiol	CH_3CH_2SH	10.6
phenol	C_6H_5OH	9.95
acetic acid	CH_3CO_2H	4.76
trifluoroacetic acid	CF_3CO_2H	0.23

***2.43** Scientists have determined that the acidity of the upper-ocean has increased an average of 30%, going from a p*H* value of 8.2 to 8.1 over a 250 year period. This increase in acidity is attributed to increased CO_2 levels, which in turn affects the availability of CO_3^{2-}. With this in mind, discuss the following as a group:

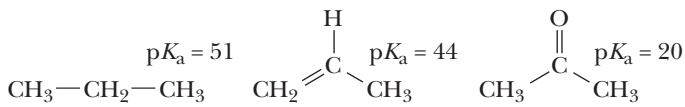
(a) Explain the relationship between the p*H* of seawater and the availability of carbonate ion. Does the change in p*H* from 8.2 to 8.1 increase or decrease the availability of carbonate ion?

(b) Using your knowledge of acid–base chemistry, complete the equations in the diagram below to show how CO_2 levels influence the availability of CO_3^{2-} in seawater.



(c) How would a decrease in available carbonate ion, CO_3^{2-}, affect marine organisms' ability to build and maintain shells and other body parts from calcium carbonate?

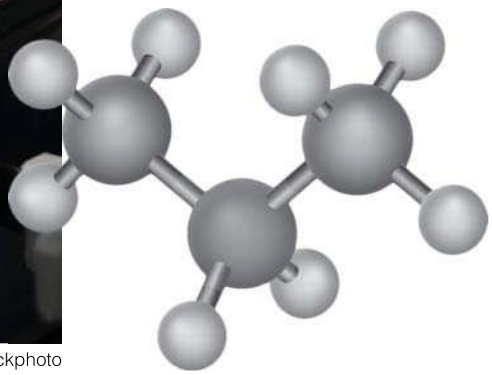
2.44 The pK_a of a CH_3 proton on propane is 51. The pK_a values for the CH_3 protons on propene and acetone are considerably lower. Discuss why these CH_3 protons are so much more acidic. Use drawings to inform your discussion.



propane propene acetone

© Lauri Patterson/iStockphoto

Alkanes and Cycloalkanes



3

The burners of gas grills are fueled by liquefied petroleum gas (LPG). LPG contains mostly propane, which is how their containers became known as "propane tanks," but LPG also contains small amounts of ethane, propene, and butane. Inset: A model of propane.

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

PERHAPS YOU HAVE HEARD of the term **hydrocarbon**? It is often used by the media when discussing petroleum and other fossil fuels. Figure 3.1, however, shows that hydrocarbons are actually a larger class of organic compound, all entirely composed of only hydrogen and carbon. The word "saturated" is another often used term, especially in the food industry (think "saturated fats"). **Saturated** compounds are molecules whose carbon chains contain only carbon–carbon single bonds. They are categorized as such because "saturated" carbons, carbons that have the maximum number of hydrogens bonded to them, are relatively unreactive. This is why saturated fats are considered unhealthy; their hydrocarbon chains require more energy to break down or digest.

Hydrocarbon A compound that contains only carbon atoms and hydrogen atoms.

Saturated hydrocarbon A hydrocarbon containing only carbon–carbon single bonds.

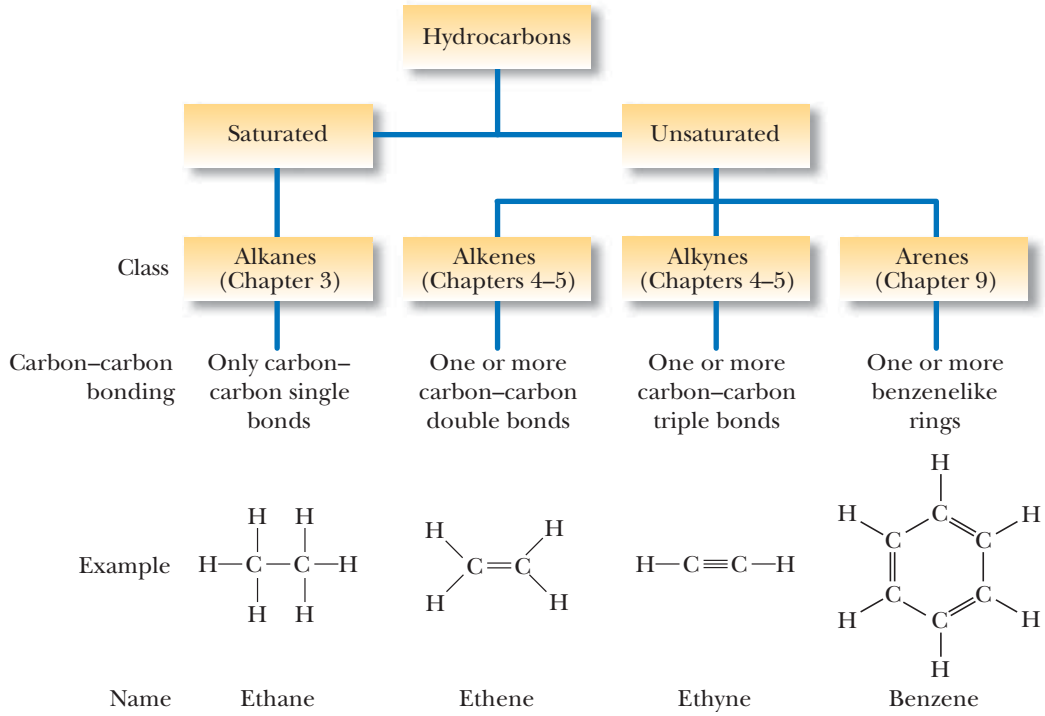


FIGURE 3.1 The four classes of hydrocarbons.

Unsaturated hydrocarbon A hydrocarbon containing at least one carbon–carbon pi bond.

Alkane A saturated hydrocarbon whose carbon atoms are arranged in an open chain.

Unsaturated hydrocarbons, on the other hand, have at least one carbon–carbon pi bond. Alkenes, alkynes, and arenes are all specific types of unsaturated hydrocarbons. Recall from Chapter 1 that carbon–carbon pi bonds are weaker than carbon–carbon sigma bonds. Their weaker pi bonds make them more reactive, and we will soon see why their structural features set them apart from the **alkanes** we study in this chapter.

3.1 What Are Alkanes?

Methane (CH_4) and ethane (C_2H_6) are the smallest members of the alkane family. Figure 3.2 shows molecular formulas, Lewis structures, and ball-and-stick models for these molecules. The shape of methane is tetrahedral, and all H—C—H bond angles are 109.5°. Each carbon atom in ethane is also tetrahedral, and all bond angles are approximately 109.5°.

Although the three-dimensional shapes of larger alkanes are more complex than those of methane and ethane, the four bonds about each carbon atom are still arranged in a tetrahedral manner, and all bond angles are still approximately 109.5°.

The next members of the alkane family are propane, butane, and pentane. In the representations that follow, these hydrocarbons are drawn first as condensed structural formulas that show all carbons and hydrogens. They are then drawn in an even more abbreviated form called a **line-angle formula**. In this type of representation, a line represents a carbon–carbon bond, and an angle represents a carbon atom. A line ending

Charles D. Winters

Butane is the fuel in this lighter. Butane molecules are present in the liquid and gaseous states in the lighter.

Line-angle formula An abbreviated way to draw structural formulas in which each vertex and each line ending represents a carbon atom and a line represents a bond.

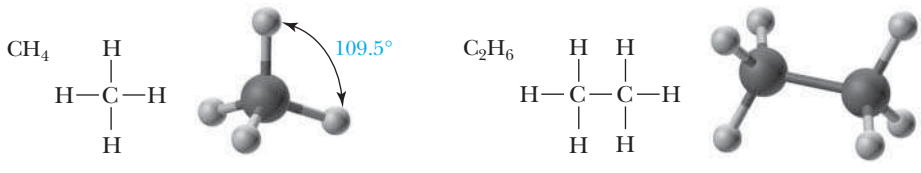
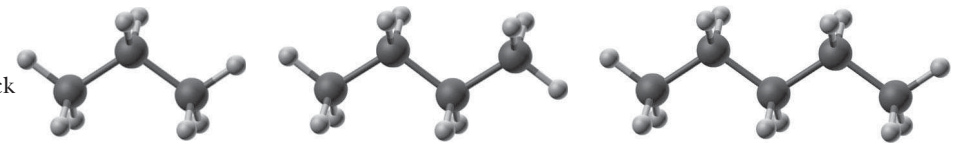


FIGURE 3.2 Methane and ethane.

represents a —CH_3 group. Although hydrogen atoms are not shown in line-angle formulas, they are assumed to be there in sufficient numbers to give each carbon four bonds.



	Propane	Butane	Pentane
Ball-and-stick model			
Line-angle formula			
Condensed structural formula	$CH_3CH_2CH_3$	$CH_3CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2CH_3$

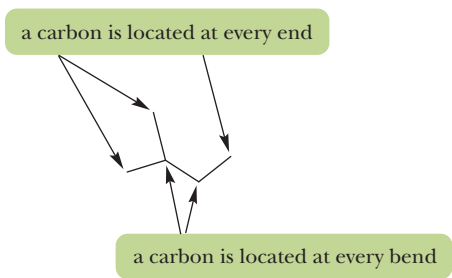
line-angle formulas do not show carbon or hydrogen labels

We can write structural formulas for alkanes in still another abbreviated form. The structural formula of pentane, for example, contains three CH_2 (methylene) groups in the middle of the chain. We can collect these groups together and write the structural formula as $CH_3(CH_2)_3CH_3$. Table 3.1 gives the names and molecular formulas of the first 20 alkanes. Note that the names of all these alkanes end in *-ane*. We will have more to say about naming alkanes in Section 3.3.

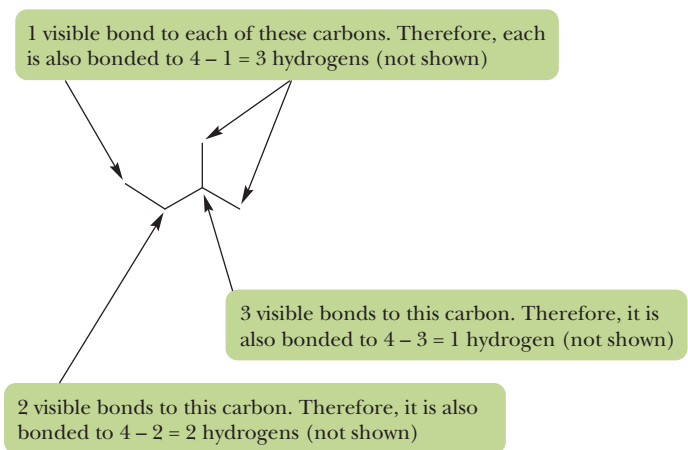
Interpret Line-Angle Formulas

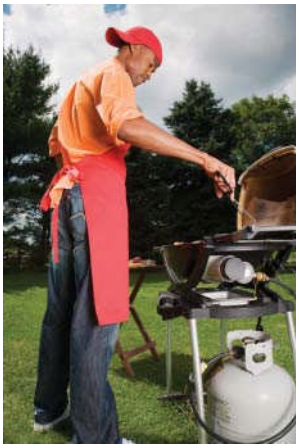
HOW TO 3.1

Use the mnemonic "a carbon at every *bend* and at every *end*. . . ."



Because carbon requires four bonds to satisfy its valency, count the number of visible bonds to each carbon and then subtract this number from 4 to determine the number of hydrogens also bonded to that carbon (but not shown).





Media Bakery

A tank for propane fuel.

TABLE 3.1 Names, Molecular Formulas, and Condensed Structural Formulas for the First 20 Alkanes with Unbranched Chains

Name	Molecular Formula	Condensed Structural Formula	Name	Molecular Formula	Condensed Structural Formula
methane	CH_4	CH_4	undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
ethane	C_2H_6	CH_3CH_3	dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
propane	C_3H_8	$CH_3CH_2CH_3$	tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$	tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$	pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$	hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$	heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$	octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$
nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$	nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

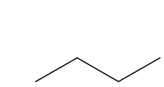
Alkanes have the general molecular formula C_nH_{2n+2}. Thus, given the number of carbon atoms in an alkane, it is easy to determine the number of hydrogens in the molecule and also its molecular formula. For example, decane, with 10 carbon atoms, must have $(2 \times 10) + 2 = 22$ hydrogens and the molecular formula $C_{10}H_{22}$.

3.2 What Is Constitutional Isomerism in Alkanes?

Constitutional isomers
Compounds with the same molecular formula, but a different order of attachment (connectivity) of their atoms.

Constitutional isomers are compounds that have the same molecular formula, but different structural formulas. By "different structural formulas," we mean that these compounds differ in the kinds of bonds they have (single, double, or triple) or in their connectivity (the order of attachment among their atoms).

For the molecular formulas CH_4, C_2H_6, and C_3H_8, only one order of attachment of atoms is possible. For the molecular formula C_4H_{10}, two orders of attachment of atoms are possible. In one of these, named butane, the four carbons are bonded in a chain; in the other, named 2-methylpropane, three carbons are bonded in a chain, with the fourth carbon as a branch on the middle carbon of the chain.

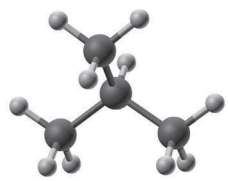


$CH_3CH_2CH_2CH_3$

Butane
(boiling point
= –0.5 °C)

CH_3CHCH_3
|
CH_3

2-Methylpropane
(boiling point
= –11.6 °C)



Butane and 2-methylpropane are constitutional isomers; they are different compounds and have different physical and chemical properties. Their boiling points, for example, differ by approximately 11°C. We will discuss how to name alkanes in the next section.

In Section 1.7, we encountered several examples of constitutional isomers, although we did not call them that at the time. We saw that there are two alcohols with the molecular formula C_3H_8O, two aldehydes with the molecular formula C_4H_8O, and two carboxylic acids with the molecular formula $C_4H_8O_2$.

To find out whether two or more structural formulas represent constitutional isomers, write the molecular formula of each and then compare them. All compounds that have the same molecular formula, but different structural formulas, are constitutional isomers.

EXAMPLE 3.1

Do the structural formulas in each pair represent the same compound or constitutional isomers?

(a) $CH_3CH_2CH_2CH_2CH_2CH_3$ and $CH_3CH_2CH(CH_2CH_2CH_3)$ (each is C_6H_{14})

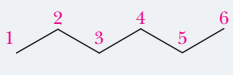
(b) $CH_3CHCH_2CH(CH_3)CH_3$ and $CH_3CH_2CH(CH_3)CHCH_3$ (CH_3) (each is C_7H_{16})

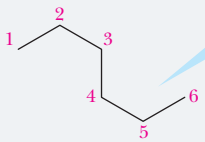
STRATEGY

To determine whether these structural formulas represent the same compound or constitutional isomers, first find the longest chain of carbon atoms in each. Note that it makes no difference whether the chain is drawn straight or bent. Second, number the longest chain from the end nearest the first branch. Third, compare the lengths of each chain and the sizes and locations of any branches. Structural formulas that have the same connectivity of atoms represent the same compound; those that have a different connectivity of atoms represent constitutional isomers.

SOLUTION

(a) Each structural formula has an unbranched chain of six carbons. The two structures are identical and represent the same compound:

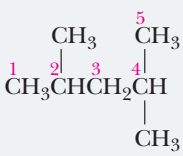




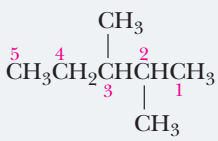
do not let the direction in which the chain or substituents are drawn distract you. When determining constitutional isomerism, connectivity of atoms is key.

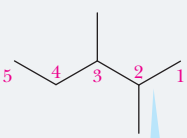
$CH_3CH_2CH_2CH_2CH_2CH_3$ and $CH_3CH_2CH(CH_2CH_2CH_3)$

(b) Each structural formula has a chain of five carbons with two CH_3 branches. Although the branches are identical, they are at different locations on the chains. Therefore, these structural formulas represent constitutional isomers:



and





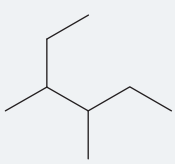
do not let the direction in which the chain or substituents are drawn distract you. When determining constitutional isomerism, connectivity of atoms is key.

See problems 3.17–3.20, 3.22

PROBLEM 3.1

Do the structural formulas in each pair represent the same compound or constitutional isomers?

(a)



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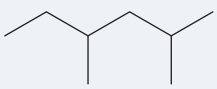
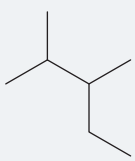


(b)



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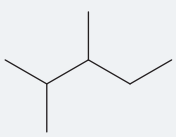


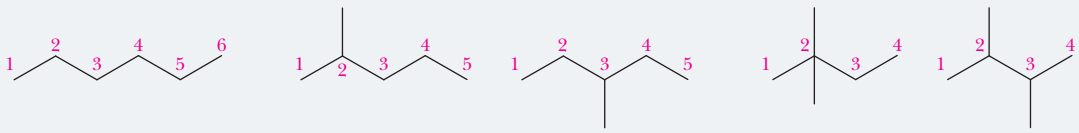
EXAMPLE 3.2

Draw structural formulas for the five constitutional isomers with the molecular formula C_6H_{14}.

STRATEGY

In solving problems of this type, you should devise a strategy and then follow it. Here is one such strategy: First, draw a line-angle formula for the constitutional isomer with all six carbons in an unbranched chain. Then, draw line-angle formulas for all constitutional isomers with five carbons in a chain and one carbon as a branch on the chain. Finally, draw line-angle formulas for all constitutional isomers with four carbons in a chain and two carbons as branches.

SOLUTION



Six carbons in an unbranched chain

Five carbons in a chain; one carbon as a branch

Four carbons in a chain; two carbons as branches

No constitutional isomers with only three carbons in the longest chain are possible for C_6H_{14}.

See problems 3.21, 3.23

PROBLEM 3.2

Draw structural formulas for the three constitutional isomers with molecular formula C_5H_{12}.

The ability of carbon atoms to form strong, stable bonds with other carbon atoms results in a staggering number of constitutional isomers. As the following table shows, there are 3 constitutional isomers with the molecular formula C_5H_{12}, 75 constitutional isomers with the molecular formula $C_{10}H_{22}$, and almost 37 million constitutional isomers with the molecular formula $C_{25}H_{52}$:

Carbon Atoms	Constitutional Isomers
1	0
5	3
10	75
15	4,347
25	36,797,588

Thus, for even a small number of carbon and hydrogen atoms, a very large number of constitutional isomers is possible. In fact, the potential for structural and functional group individuality among organic molecules made from just the basic building blocks of carbon, hydrogen, nitrogen, and oxygen is practically limitless.

3.3 How Do We Name Alkanes?

A. The IUPAC System of Organic Nomenclature

Nomenclature A set of rules for naming organic compounds.

Ideally, every organic compound should have a name from which its structural formula can be drawn. For this purpose, chemists have adopted a set of rules, or **nomenclature**, established by an organization called the International Union of Pure and Applied Chemistry (IUPAC).

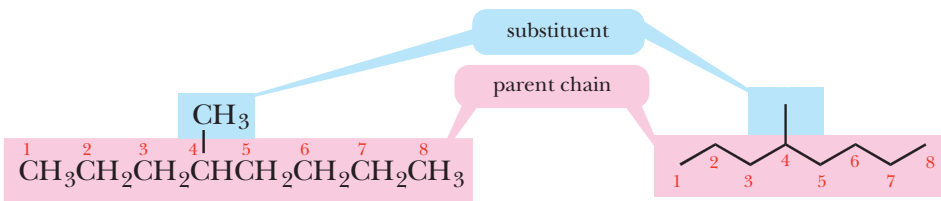
The IUPAC name of an alkane with an unbranched chain of carbon atoms consists of two parts: (1) a prefix that indicates the number of carbon atoms in the chain and (2) the ending **-ane** to show that the compound is a saturated hydrocarbon. Table 3.2 gives the prefixes used to show the presence of 1 to 20 carbon atoms.

The first four prefixes listed in Table 3.2 were chosen by the IUPAC because they were well established even before there were hints of the structural theory underlying the discipline. For example, the prefix *but-* appears in the name *butyric acid*, a compound of four carbon atoms formed by the air oxidation of butter fat (Latin: *butyrum*, butter). Prefixes to show five or more carbons are derived from Greek or Latin numbers. (See Table 3.1 for the names, molecular formulas, and condensed structural formulas for the first 20 alkanes with unbranched chains.)

TABLE 3.2 Prefixes Used in the IUPAC System to Show the Presence of 1 to 20 Carbons in an Unbranched Chain

Prefix	Number of Carbon Atoms	Prefix	Number of Carbon Atoms
meth-	1	undec-	11
eth-	2	dodec-	12
prop-	3	tridec-	13
but-	4	tetradec-	14
pent-	5	pentadec-	15
hex-	6	hexadec-	16
hept-	7	heptadec-	17
oct-	8	octadec-	18
non-	9	nonadec-	19
dec-	10	eicos-	20

The IUPAC name of an alkane with a branched chain consists of a **parent name** that indicates the longest chain of carbon atoms in the compound and substituent names that indicate the groups bonded to the parent chain.



4-Methyloctane

A substituent group derived from an alkane by the removal of a hydrogen atom is called an **alkyl group** and is commonly represented by the symbol **R-**. We name alkyl groups by dropping the *-ane* from the name of the parent alkane and adding the suffix *-yl*. Table 3.3 gives the names and structural formulas for eight of the most common alkyl groups. The prefix *sec-* is an abbreviation for secondary, meaning a carbon bonded to two other carbons. The prefix *tert-* is an abbreviation for tertiary, meaning a carbon bonded to three other carbons. Note that when these two prefixes are part of a name, they are always italicized.

Alkyl group A group derived by removing a hydrogen from an alkane; given the symbol R-.

R- A symbol used to represent an alkyl group.

The rules of the IUPAC system for naming alkanes are as follows:

1. The name for an alkane with an unbranched chain of carbon atoms consists of a prefix showing the number of carbon atoms in the chain and the ending *-ane*.

2. For branched-chain alkanes, take the longest chain of carbon atoms as the parent chain, and its name becomes the root name.

TABLE 3.3 Names of the Most Common Alkyl Groups

Name	Condensed Structural Formula	Name	Condensed Structural Formula
methyl	$-CH_3$	isobutyl	$-CH_2CH(CH_3)_2$
ethyl	$-CH_2CH_3$	*sec*-butyl	$-CH(CH_3)CH_2CH_3$
propyl	$-CH_2CH_2CH_3$	*tert*-butyl	$-C(CH_3)_3$
isopropyl	$-CH(CH_3)_2$		
butyl	$-CH_2CH_2CH_2CH_3$		

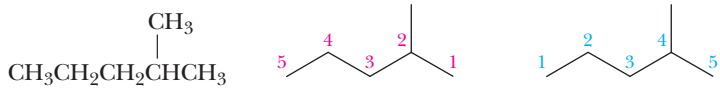
abbreviation for "secondary"

abbreviation for "tertiary"

3. Give each substituent on the parent chain a name and a number. The number shows the carbon atom of the parent chain to which the substituent is bonded. Use a hyphen to connect the number to the name:

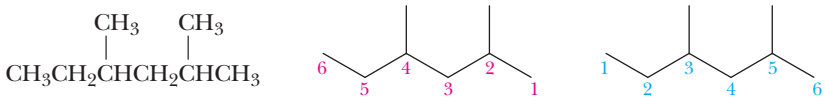
2-Methylpropane

4. If there is one substituent, number the parent chain from the end that gives it the lower number:



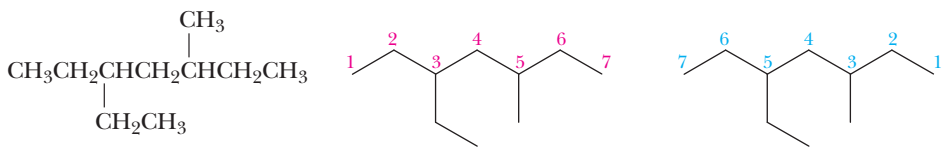
2-Methylpentane (not 4-methylpentane)

5. If there are two or more identical substituents, number the parent chain from the end that gives the lower number to the substituent encountered first. The number of times the substituent occurs is indicated by the prefix *di-*, *tri-*, *tetra-*, *penta-*, *hexa-*, and so on. A comma is used to separate position numbers:



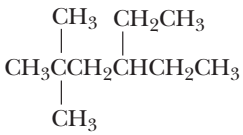
2,4-Dimethylhexane (not 3,5-dimethylhexane)

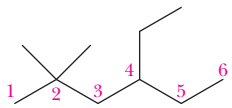
6. If there are two or more different substituents, list them in alphabetical order, and number the chain from the end that gives the lower number to the substituent encountered first. If there are different substituents in equivalent positions on opposite ends of the parent chain, the substituent of lower alphabetical order is given the lower number:



3-Ethyl-5-methylheptane (not 3-methyl-5-ethylheptane)

7. The prefixes *di-*, *tri-*, *tetra-*, and so on are not included in alphabetizing. Neither are the hyphenated prefixes *sec-* and *tert-*. "Iso," as in isopropyl, is included in alphabetizing. Alphabetize the names of the substituents first, and then insert the prefix. In the following example, the alphabetizing parts are ethyl and methyl, not ethyl and dimethyl:

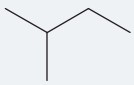


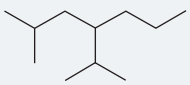


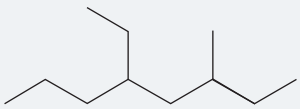
4-Ethyl-2,2-dimethylhexane
(not 2,2-dimethyl-4-ethylhexane)

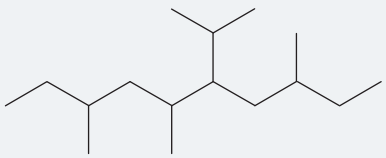
EXAMPLE 3.3

Write IUPAC names for these alkanes:

(a) 

(b) 

(c) 

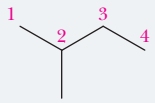
(d) 

STRATEGY

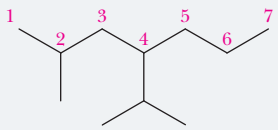
First determine the root name of the alkane. Then name the substituents and place them in alphabetical order. Number the parent chain so as to give the lower number to the substituents encountered first. If substituents have equivalent positions, the lower number is assigned to the substituents with the lower alphabetical order.

See problems 3.24, 3.25, 3.28

SOLUTION

(a) 

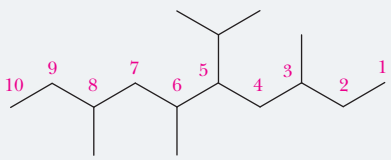
2-Methylbutane

(b) 

4-Isopropyl-2-methylheptane

(c) 

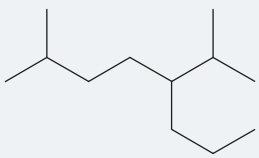
5-Ethyl-3-methyloctane

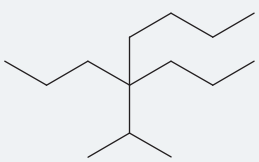
(d) 

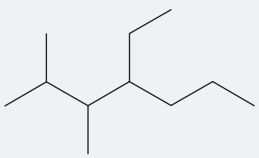
5-Isopropyl-3,6,8-trimethyldecane
(not 6-isopropyl-3,5,8-trimethyldecane)

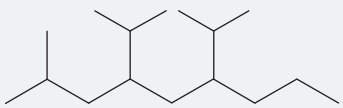
PROBLEM 3.3

Write IUPAC names for these alkanes:

(a) 

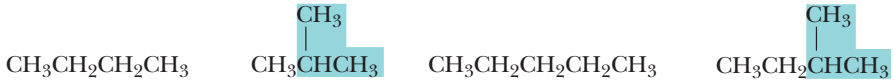
(b) 

(c) 

(d) 

B. Common Names

In the older system of common nomenclature, the total number of carbon atoms in an alkane, regardless of their arrangement, determines the name. The first three alkanes are methane, ethane, and propane. All alkanes with the molecular formula C_4H_{10} are called butanes, all those with the molecular formula C_5H_{12} are called pentanes, and all those with the molecular formula C_6H_{14} are called hexanes. For alkanes beyond propane, *iso* indicates that one end of an otherwise unbranched chain terminates in a $(CH_3)_2CH—$group. Following are examples of common names:

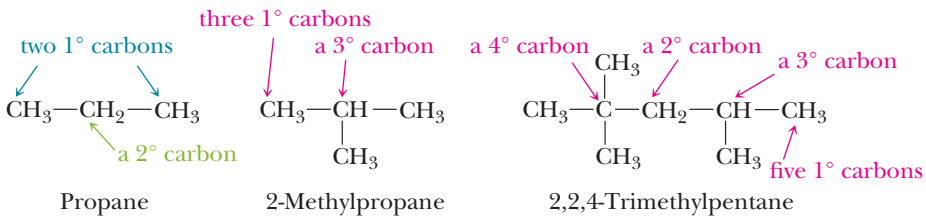


This system of common names has no good way of handling other branching patterns, so, for more complex alkanes, it is necessary to use the more flexible IUPAC system of nomenclature.

In this text, we concentrate on IUPAC names. However, we also use common names, especially when the common name is used almost exclusively in the everyday discussions of chemists and biochemists. When both IUPAC and common names are given in the text, we always give the IUPAC name first, followed by the common name in parentheses. In this way, you should have no doubt about which name is which.

C. Classification of Carbon and Hydrogen Atoms

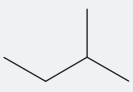
We classify a carbon atom as primary (1°), secondary (2°), tertiary (3°), or quaternary (4°), depending on the number of carbon atoms bonded to it. A carbon bonded to one carbon atom is a primary carbon; a carbon bonded to two carbon atoms is a secondary carbon, and so forth, as shown in the following:

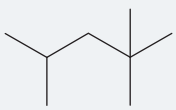


Similarly, hydrogens are also classified as primary, secondary, or tertiary, depending on the type of carbon to which each is bonded. Those bonded to a primary carbon are classified as primary hydrogens, those on a secondary carbon are secondary hydrogens, and those on a tertiary carbon are tertiary hydrogens.

EXAMPLE 3.4

Classify each carbon atom in the following compounds as 1°, 2°, 3°, or 4°.

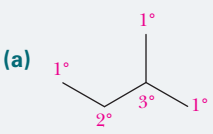
(a) 

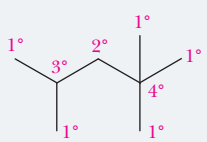
(b) 

STRATEGY

To classify carbons, determine whether each is bonded to 1 carbon (1°), 2 carbons (2°), 3 carbons (3°), or 4 carbons (4°).

SOLUTION

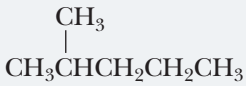
(a) 

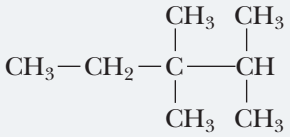
(b) 

See problems 3.26, 3.27

PROBLEM 3.4

Classify each hydrogen atom in the following compounds as 1°, 2°, or 3°.

(a) 

(b) 

3.4 What Are Cycloalkanes?

A hydrocarbon that contains carbon atoms joined to form a ring is called a *cyclic hydrocarbon*. When all carbons of the ring are saturated, we call the hydrocarbon a **cycloalkane**. Cycloalkanes of ring sizes ranging from 3 to over 30 abound in nature, and, in principle, there is no limit to ring size. Five-membered (cyclopentane) and six-membered (cyclohexane) rings are especially abundant in nature and have received special attention.

Cycloalkane A saturated hydrocarbon that contains carbon atoms joined to form a ring.

Figure 3.3 shows the structural formulas of cyclobutane, cyclopentane, and cyclohexane. When writing structural formulas for cycloalkanes, chemists rarely show all carbons and hydrogens. Rather, they use line-angle formulas to represent cycloalkane rings. Each ring is represented by a regular polygon having the same number of sides as there are carbon atoms in the ring. For example, chemists represent cyclobutane by a square, cyclopentane by a pentagon, and cyclohexane by a hexagon.

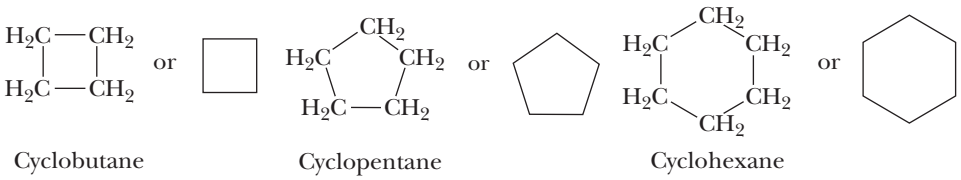


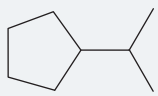
FIGURE 3.3 Examples of cycloalkanes.

Cycloalkanes contain two fewer hydrogen atoms than an alkane with the same number of carbon atoms. For instance, compare the molecular formulas of cyclohexane (C_6H_{12}) and hexane (C_6H_{14}). The general formula of a cycloalkane is C_nH_{2n}.

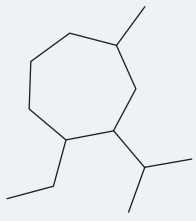
To name a cycloalkane, prefix the name of the corresponding open-chain hydrocarbon with *cyclo-*, and name each substituent on the ring. If there is only one substituent, there is no need to give it a number. If there are two substituents, number the ring by beginning with the substituent of lower alphabetical order. If there are three or more substituents, number the ring so as to give them the lowest set of numbers, and then list the substituents in alphabetical order.

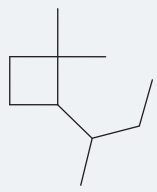
EXAMPLE 3.5

Write the molecular formula and IUPAC name for each cycloalkane.

(a) 

(b) 

(c) 

(d) 

STRATEGY

First determine the root name of the cycloalkane. Then name the substituents and place them in alphabetical order. Number the parent chain so as to give the lower number to the substituent encountered first. If substituents have equivalent positions, the lower number is assigned to the substituent with the lower alphabetical order.

SOLUTION

(a) The molecular formula of this cycloalkane is C_8H_{16}. Because there is only one substituent on the ring, there is no need to number the atoms of the ring. The IUPAC name of this compound is isopropylcyclopentane.

(b) Number the atoms of the cyclohexane ring by beginning with *tert*-butyl, the substituent of lower alphabetical order. The compound's name is 1-*tert*-butyl-4-methylcyclohexane, and its molecular formula is $C_{11}H_{22}$.

recall that *tert* is not considered when alphabetizing substituents

(c) The molecular formula of this cycloalkane is $C_{13}H_{26}$. The compound's name is 1-ethyl-2-isopropyl-4-methylcycloheptane. The ethyl group is numbered 1 because this allows the isopropyl group to be encountered sooner than if the methyl group were numbered 1.

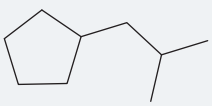
recall that "iso" is considered when alphabetizing substituents. The numbering pattern 1,2,4 is preferred over 1,3,4 or 1,5,7

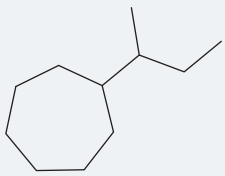
(d) The molecular formula of this cycloalkane is $C_{10}H_{20}$. The compound's name is 2-*sec*-butyl-1,1-dimethylcyclobutane. This example illustrates that "*sec*" and "di" are not used in alphabetizing for nomenclature.

See problems 3.24, 3.25, 3.28

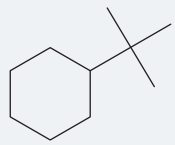
PROBLEM 3.5

Write the molecular formula and IUPAC name for each cycloalkane:

(a) 

(b) 

(c) 

(d) 

3.5 How Is the IUPAC System of Nomenclature Applied to Molecules that Contain Functional Groups?

The naming of alkanes and cycloalkanes in Sections 3.3 and 3.4 illustrates the application of the IUPAC system of nomenclature to these two specific classes of organic compounds. Now let us describe the general approach of the IUPAC system. The name we give to any compound with a chain of carbon atoms consists of three parts: a prefix, an infix (a modifying element inserted into a word), and a suffix. Each part provides specific information about the structural formula of the compound.

1. The prefix shows the number of carbon atoms in the parent chain. Prefixes that show the presence of 1 to 20 carbon atoms in a chain were given in Table 3.2.

2. The infix shows the nature of the carbon–carbon bonds in the parent chain:

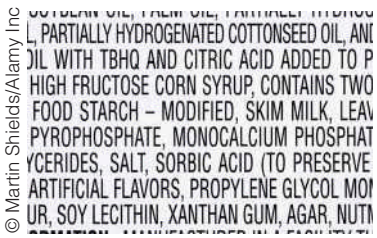
Infix	Nature of Carbon–Carbon Bonds in the Parent Chain
-an-	all single bonds
-en-	one or more double bonds
-yn-	one or more triple bonds

keep in mind that the infix refers to the nature of the *C–C bonds in the parent chain*

3. The suffix shows the class of compound to which the substance belongs:

Suffix	Class of Compound
-e	hydrocarbon
-ol	alcohol
-al	aldehyde
-one	ketone
-oic acid	carboxylic acid

we will learn suffixes for other classes of compounds in later chapters



Nomenclature allows us to readily identify organic compounds, for example, as additives in foods.

EXAMPLE 3.6

Following are IUPAC names and structural formulas for four compounds:

(a) $CH_2{=}CHCH_3$ Propene **(b)** CH_3CH_2OH Ethanol **(c)** $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}OH$ Pentanoic acid **(d)** $HC{\equiv}CH$ Ethyne

Divide each name into a prefix, an infix, and a suffix, and specify the information about the structural formula that is contained in each part of the name.

STRATEGY

First look at the first few letters of the name (meth, eth, prop, but, etc.). This is the prefix that tells the number of carbons in the parent chain. Next look at "an," "en," or "yn." These infixes indicate the nature of the carbon–carbon bonds in the parent chain. The letters that follow the infix are part of the suffix, which determines the class of compound to which the molecule belongs.

SOLUTION

(a) propene — a carbon–carbon double bond; three carbon atoms; a hydrocarbon

(b) ethanol — only carbon–carbon single bonds; two carbon atoms; an alcohol

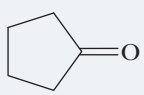
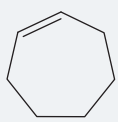
(c) pentanoic acid — only carbon–carbon single bonds; five carbon atoms; a carboxylic acid

(d) ethyne — a carbon–carbon triple bond; two carbon atoms; a hydrocarbon

See problems 3.29, 3.30

PROBLEM 3.6

Combine the proper prefix, infix, and suffix, and write the IUPAC name for each compound:

(a) $CH_3\overset{\overset{O}{\|}}{C}CH_3$ **(b)** $CH_3CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}H$ **(c)**  **(d)** 

3.6 What Are the Conformations of Alkanes and Cycloalkanes?

Even though structural formulas are useful for showing the order of attachment of atoms, they do not show three-dimensional shapes. As chemists try to understand more and more about the relationships between structure and the chemical and physical properties of molecules, it becomes increasingly important to know more about the three-dimensional shapes of molecules.

In this section, we concentrate on ways to visualize molecules as three-dimensional objects and to visualize not only bond angles within molecules, but also distances between various atoms and groups of atoms not bonded to each other. We also describe strain, which we divide into three types: torsional strain, angle strain, and steric strain. We urge you to build models and to study and manipulate them. Organic molecules are three-dimensional objects, and it is essential that you become comfortable in dealing with them as such.

A. Alkanes

Conformation Any three-dimensional arrangement of atoms in a molecule that results by rotation about a single bond.

Staggered conformation A conformation about a carbon–carbon single bond in which the atoms on one carbon are as far apart as possible from the atoms on the adjacent carbon.

Newman projection A way to view a molecule by looking along a carbon–carbon bond.

Alkanes with two or more carbons can be twisted into a number of different three-dimensional arrangements of their atoms by rotating about one or more carbon–carbon bonds. Any three-dimensional arrangement of atoms that results from rotation about a single bond is called a **conformation**. Figure 3.4(a) shows a ball-and-stick model of a **staggered conformation** of ethane. In this conformation, the three C—H bonds on one carbon are as far apart as possible from the three C—H bonds on the adjacent carbon. Figure 3.4(b), called a **Newman projection**, is a shorthand way of representing the staggered conformation of ethane. In a Newman projection, we view a molecule along the axis of a C—C bond. The three atoms or groups of atoms nearer your eye appear on lines extending from the center of the circle at angles of 120°. The three atoms or groups of atoms on the carbon farther from your eye appear on lines extending from the circumference of the circle at angles of 120°. Remember that bond angles about each carbon in ethane are approximately 109.5° and not 120°, as this Newman projection might suggest.

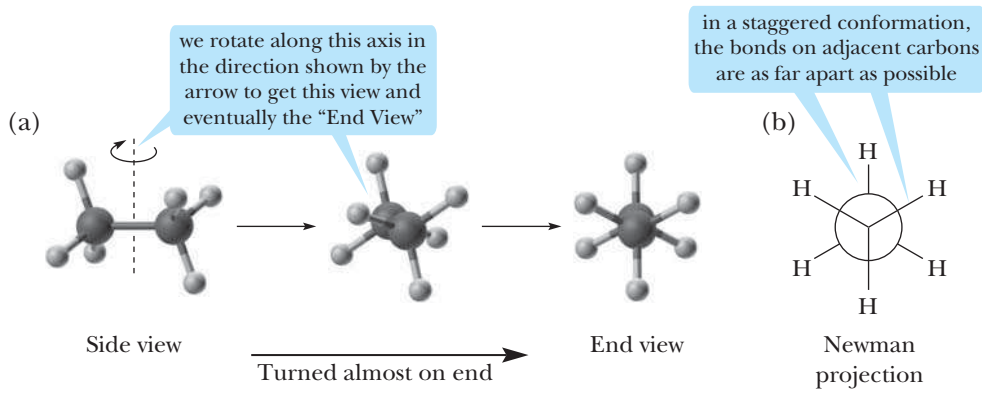
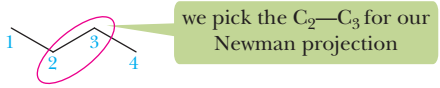


FIGURE 3.4 A staggered conformation of ethane. (a) Ball-and-stick model and (b) Newman projection.

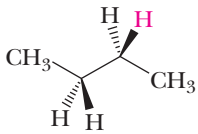
HOW TO 3.2 Visualize and Draw a Newman Projection

A Newman projection is a two-dimensional drawing of a three-dimensional molecule viewed down a carbon–carbon bond. Here are some steps you can apply when drawing Newman projections of molecules:

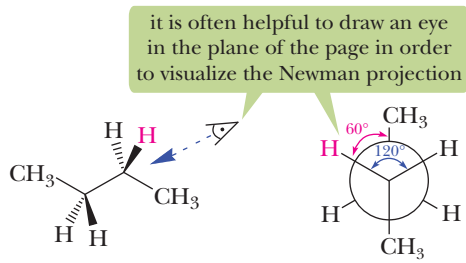
1. **Select the C–C bond you wish to look down.** Using butane as an example, let's select the C_2–C_3 bond.



2. **Draw in the hydrogens** using dashed wedges to show bonds going behind the plane of the paper and solid wedges to show bonds coming out of the plane of the paper. Hydrogens and groups that are not attached to the bond we are looking down can be shown as condensed formulas.



3. **Decide which direction to view the bond from.** Here we view the bond from right to left. The hydrogen closest to the right and coming out of the plane of the page is shown in red as a reference point.



4. Place the atoms and groups in your Newman projection. You can reference the groups to the eye that you drew. Here, the red hydrogen is to the left of the eye and pointing diagonally upward and thus ends up on the bond pointing left and diagonally upward in the Newman projection. The rightmost methyl group is pointing down relative to the eye that we drew and is therefore drawn on the vertical bond in the Newman projection. In this way, you can accurately draw in the remaining atoms and groups. This molecule turns out to be in a staggered conformation.

Figure 3.5 shows a ball-and-stick model and a Newman projection of an **eclipsed conformation** of ethane. In this conformation, the three C—H bonds on one carbon are as close as possible to the three C—H bonds on the adjacent carbon. In other words, hydrogen atoms on the back carbon are eclipsed by the hydrogen atoms on the front carbon.

Eclipsed conformation A conformation about a carbon–carbon single bond in which the atoms on one carbon are as close as possible to the atoms on the adjacent carbon.

For a long time, chemists believed that rotation about the C—C single bond in ethane was completely free. Studies of ethane and other molecules, however, have shown that a potential energy difference exists between its staggered and eclipsed conformations and that rotation is not completely free. In ethane, the potential energy of the eclipsed conformation is a maximum and that of the staggered conformation is a minimum. The difference in potential energy between these two conformations is approximately 12.6 kJ/mol (3.0 kcal/mol).

The strain induced in the eclipsed conformation of ethane is an example of torsional strain. **Torsional strain** (also called eclipsed interaction strain) is strain that arises when nonbonded atoms separated by three bonds are forced from a staggered conformation to an eclipsed conformation.

Torsional strain (also called eclipsed interaction strain) Strain that arises when atoms separated by three bonds are forced from a staggered conformation to an eclipsed conformation.

Side view Turned almost on end Newman projection

FIGURE 3.5 An eclipsed conformation of ethane. (a, b) Ball-and-stick models and (c) Newman projection.

EXAMPLE 3.7

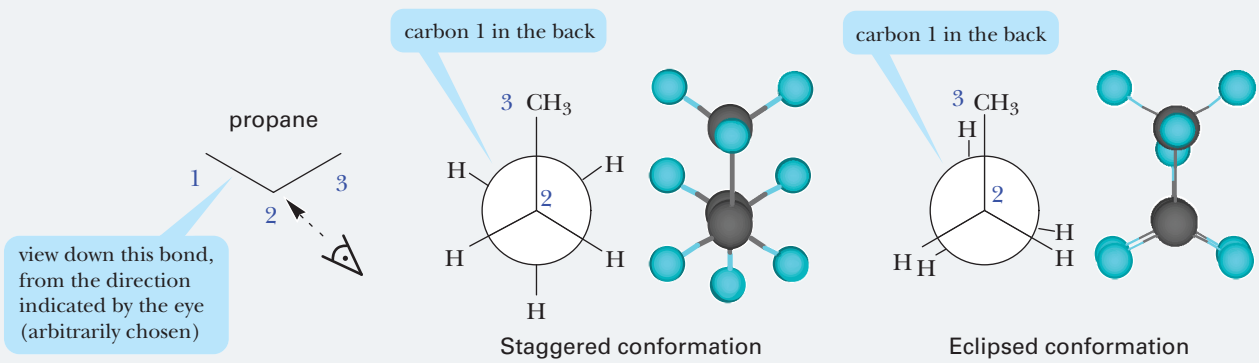
Draw Newman projections for one staggered conformation and one eclipsed conformation of propane.

STRATEGY

Draw the line-angle formula of propane and choose a bond along which to view for the Newman projection. Keep track of the carbons in the line-angle formula and in the Newman projection (numbering them helps). Draw the staggered and eclipsed Newman projections and complete them by adding in the carbons and hydrogens.

SOLUTION

Following are Newman projections and ball-and-stick models of these conformations:



Staggered conformation Eclipsed conformation

See problems 3.32, 3.37

PROBLEM 3.7

Draw Newman projections for two staggered and two eclipsed conformations of 1,2-dichloroethane.

B. Cycloalkanes

We limit our discussion to the conformations of cyclopentanes and cyclohexanes because these are the most common carbon rings in the molecules of nature.

Cyclopentane

We can draw cyclopentane [Figure 3.6(a)] as a planar conformation with all C—C—C bond angles equal to 108° [Figure 3.6(b)]. This angle differs only slightly from the tetrahedral angle of 109.5°; consequently, there is little angle strain in the planar conformation of cyclopentane. **Angle strain** results when a bond angle in a molecule is either expanded or compressed compared with its optimal values. There are 10 fully eclipsed C—H bonds creating a torsional strain of approximately 42 kJ/mol (10 kcal/mol). To relieve at least a part of this strain, the atoms of the ring twist into the "envelope" conformation [Figure 3.6(c)]. In this conformation, four carbon atoms are in a plane, and the fifth is bent out of the plane, rather like an envelope with its flap bent upward.

Angle strain The strain that arises when a bond angle is either compressed or expanded compared with its optimal value.

In the envelope conformation, the number of eclipsed hydrogen interactions is reduced, thereby decreasing torsional strain. The C—C—C bond angles, however, are also reduced, which increases angle strain. The observed C—C—C bond angles in cyclopentane are 105°, indicating that, in its conformation of lowest energy, cyclopentane is slightly puckered. The strain energy in cyclopentane is approximately 23.4 kJ/mol (5.6 kcal/mol).

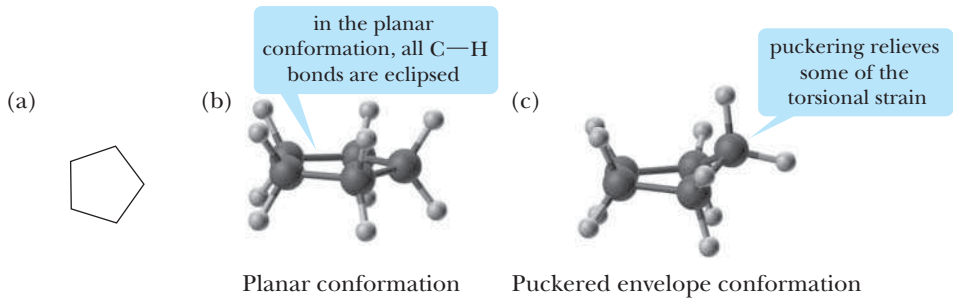


FIGURE 3.6 Cyclopentane. (a) Structural formula. (b) In the planar conformation, there are 10 pairs of eclipsed C—H interactions. (c) The most stable conformation is a puckered "envelope" conformation.

Cyclohexane

Cyclohexane adopts a number of puckered conformations, the most stable of which is a **chair conformation**. In this conformation (Figure 3.7), all C—C—C bond angles are 109.5° (minimizing angle strain), and hydrogens on adjacent carbons are staggered with respect to one another (minimizing torsional strain). Thus, there is very little strain in a chair conformation of cyclohexane.

Chair conformation The most stable puckered conformation of a cyclohexane ring; all bond angles are approximately 109.5°, and bonds to all adjacent carbons are staggered.

In a chair conformation, the C—H bonds are arranged in two different orientations. Six C—H bonds are called **equatorial bonds**, and the other six are called **axial bonds**. One way to visualize the difference between these two types of bonds is to imagine an axis through the center of the chair, perpendicular to the floor [Figure 3.8(a)]. Equatorial bonds are approximately perpendicular to our imaginary axis and alternate first slightly up and then slightly down as you move from one carbon of the ring to the next. Axial bonds are parallel to the imaginary axis. Three axial bonds point up; the other three point down. Notice that axial bonds alternate also, first up and then down as you move from one carbon of the ring to the next. Notice further that if the axial bond on a carbon points upward,

Equatorial bond A bond on a chair conformation of a cyclohexane ring that extends from the ring roughly perpendicular to the imaginary axis of the ring.

Axial bond A bond on a chair conformation of a cyclohexane ring that extends from the ring parallel to the imaginary axis of the ring.

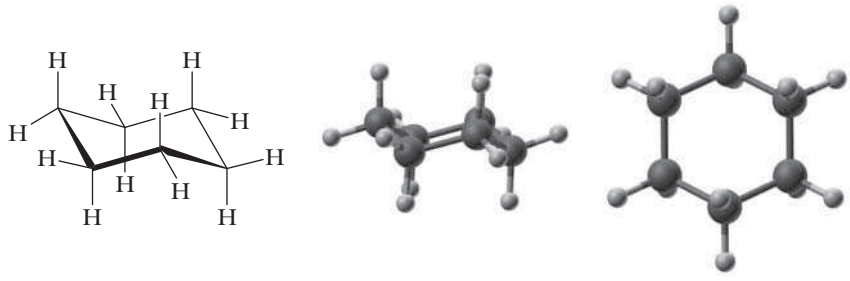
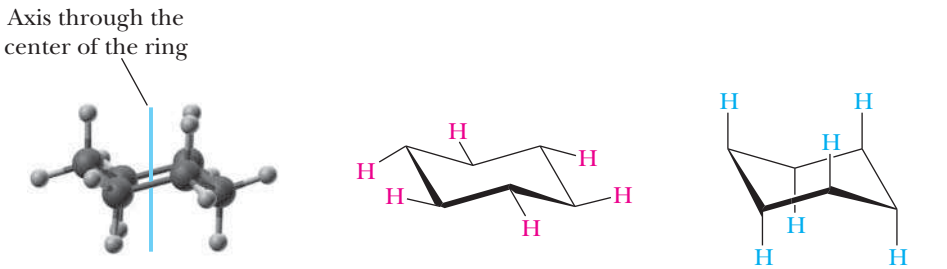


FIGURE 3.7 Cyclohexane. The most stable conformation is the puckered "chair" conformation.



(a) Ball-and-stick model showing all 12 hydrogens

(b) The six equatorial C—H bonds shown in red

(c) The six axial C—H bonds shown in blue

FIGURE 3.8 Chair conformation of cyclohexane, showing axial and equatorial C—H bonds.

HOW TO 3.3

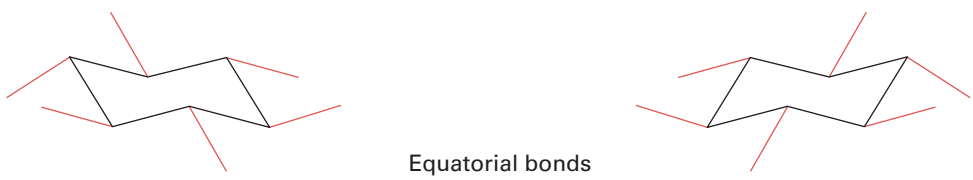
Draw Alternative Chair Conformations of Cyclohexane

You will be asked frequently to draw three-dimensional representations of chair conformations of cyclohexane and to show spatial relationships among atoms and groups of atoms bonded to the ring. Here are four steps that will help you to draw them. With a little practice you will find them easy to draw.

STEP 1: Draw two sets of parallel lines, one line in each set offset from the other in the set as shown.

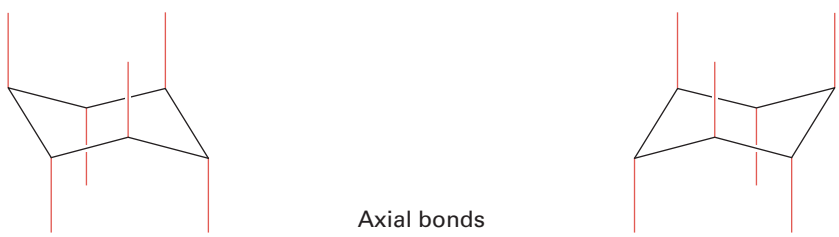
STEP 2: Complete the chair by drawing the head and foot pieces, one up and the other down.

STEP 3: Draw the equatorial bonds using ring bonds as a guide. Remember that each equatorial bond is parallel to two ring bonds, and that equatorial bonds on opposite carbons of the ring are parallel to one another. Sets of parallel equatorial and ring bonds are shown here in color.



Equatorial bonds

STEP 4: Draw the six axial bonds, as vertical lines. Remember that all axial bonds are parallel to each other. Sets of parallel axial bonds are shown in color.



Axial bonds

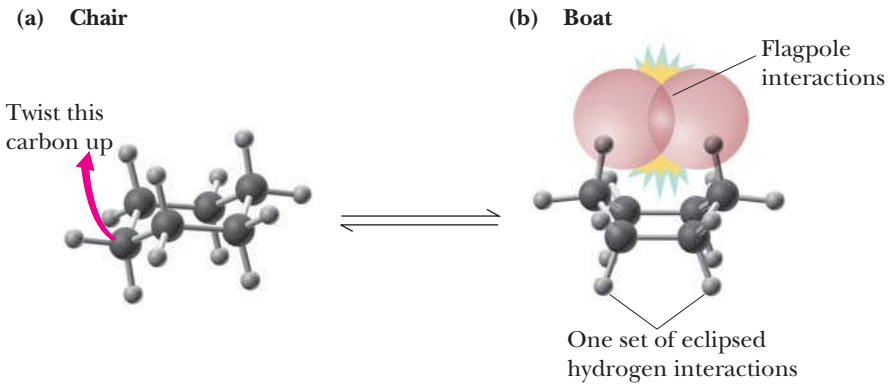


FIGURE 3.9 Conversion of (a) a chair conformation to (b) a boat conformation. In the boat conformation, there is torsional strain due to the four sets of eclipsed hydrogen interactions and steric strain due to the one set of flagpole interactions. A chair conformation is more stable than a boat conformation.

then the equatorial bond on that carbon points slightly downward. Conversely, if the axial bond on a particular carbon points downward, then the equatorial bond on that carbon points slightly upward.

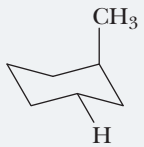
There are many other nonplanar conformations of cyclohexane, one of which is the **boat conformation**. You can visualize the interconversion of a chair conformation to a boat conformation by twisting the ring as illustrated in Figure 3.9. A boat conformation is considerably less stable than a chair conformation. In a boat conformation, torsional strain is created by four sets of eclipsed hydrogen interactions, and steric strain is created by the one set of flagpole interactions. **Steric strain** (also called nonbonded interaction strain) results when nonbonded atoms separated by four or more bonds are forced abnormally close to each other—that is, when they are forced closer than their atomic (contact) radii allow. The difference in potential energy between chair and boat conformations is approximately 27 kJ/mol (6.5 kcal/mol), which means that, at room temperature, approximately 99.99% of all cyclohexane molecules are in the chair conformation.

Boat conformation A puckered conformation of a cyclohexane ring in which carbons 1 and 4 of the ring are bent toward each other.

Steric strain The strain that arises when atoms separated by four or more bonds are forced abnormally close to one another.

EXAMPLE 3.8

Following is a chair conformation of cyclohexane showing a methyl group and one hydrogen:



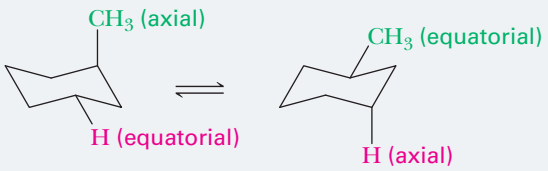
(a) Indicate by a label whether each group is equatorial or axial.

(b) Draw the other chair conformation, and again label each group as equatorial or axial.

STRATEGY

A chair-to-chair interconversion is most often done by changing the orientation of the rightmost and leftmost carbons in the chair conformation of cyclohexane. Remember that after such an interconversion, all prior axial substituents become equatorial and all prior equatorial substituents become axial.

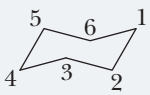
SOLUTION



See problems 3.38, 3.47

PROBLEM 3.8

Following is a chair conformation of cyclohexane with carbon atoms numbered 1 through 6:



(a) Draw hydrogen atoms that are above the plane of the ring on carbons 1 and 2 and below the plane of the ring on carbon 4.

(b) Which of these hydrogens are equatorial? Which are axial?

(c) Draw the other chair conformation. Now which hydrogens are equatorial? Which are axial? Which are above the plane of the ring, and which are below it?

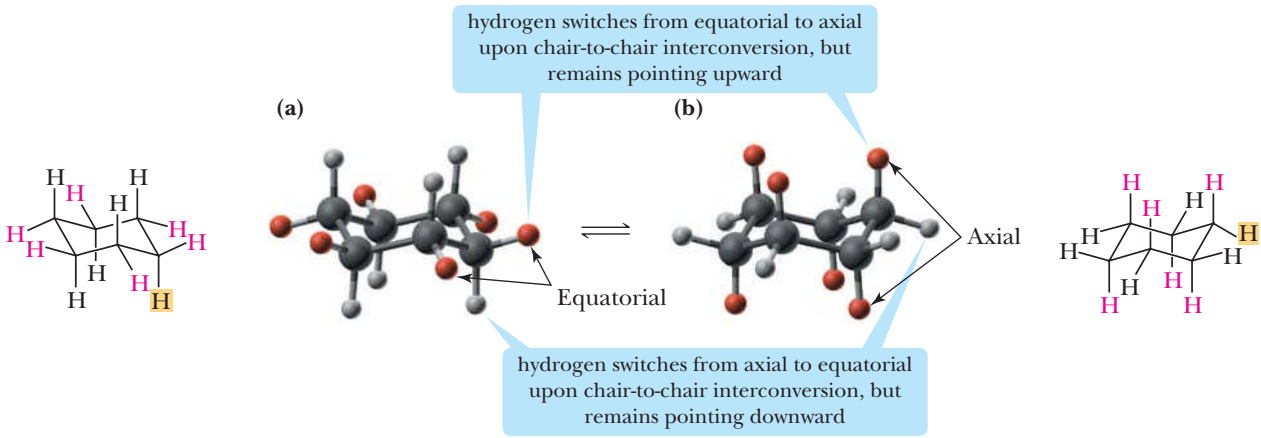


FIGURE 3.10 Interconversion of chair cyclohexanes. All C—H bonds that are equatorial in one chair are axial in the alternative chair, and vice versa.

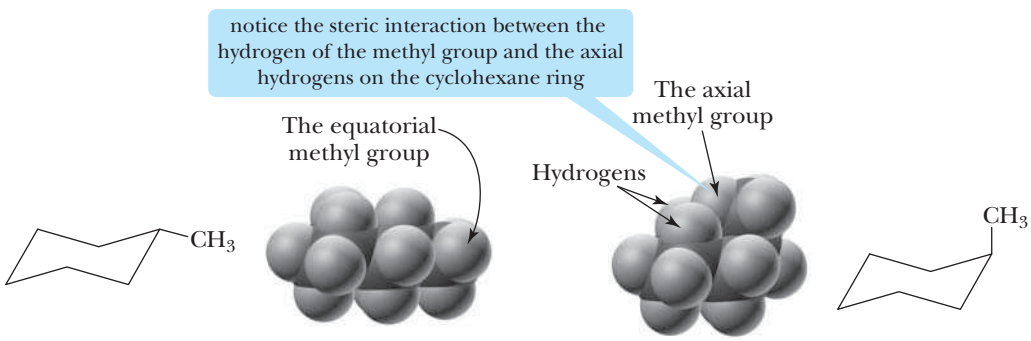
For cyclohexane, the two equivalent chair conformations can interconvert by one chair twisting first into a boat and then into the other chair. When one chair is converted to the other, a change occurs in the relative orientations in space of the hydrogen atoms bonded to each carbon: All hydrogen atoms equatorial in one chair become axial in the other, and vice versa (Figure 3.10). The interconversion of one chair conformation of cyclohexane to the other occurs rapidly at room temperature.

If we replace a hydrogen atom of cyclohexane by an alkyl group, the group occupies an equatorial position in one chair and an axial position in the other chair. This means that the two chairs are no longer equivalent and no longer of equal stability.

A convenient way to describe the relative stabilities of chair conformations with equatorial or axial substituents is in terms of a type of steric strain called **axial–axial (diaxial) interaction**. *Axial–axial interaction* refers to the steric strain existing between an axial substituent and an axial hydrogen (or other group) on the same side of the ring. Consider methylcyclohexane (Figure 3.11). When the —CH_3 is equatorial, it is staggered with respect to all other groups on its adjacent carbon atoms. When the —CH_3 is axial, it is parallel to the axial C—H bonds on carbons 3 and 5. Thus, for axial methylcyclohexane, there are two unfavorable methyl–hydrogen axial–axial interactions. For methylcyclohexane, the equatorial methyl conformation is favored over the axial methyl conformation by approximately 7.28 kJ/mol (1.74 kcal/mol). At equilibrium at room temperature, approximately 95% of all methylcyclohexane molecules have their methyl group equatorial, and less than 5% have their methyl group axial.

Diaxial interactions
Interactions between groups in parallel axial positions on the same side of a chair conformation of a cyclohexane ring.

As the size of the substituent increases, the relative amount of the conformation with the group equatorial increases. When the group is as large as *tert*-butyl, the equatorial conformation is approximately 4,000 times more abundant at room temperature than the axial conformation, and, in effect, the ring is "locked" into a chair conformation with the *tert*-butyl group equatorial.

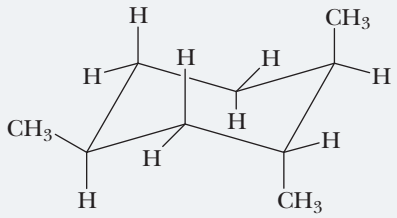


(a) Equatorial methylcyclohexane **(b)** Axial methylcyclohexane

FIGURE 3.11 Two chair conformations of methylcyclohexane. The two axial–axial interactions (steric strain) make conformation (b) less stable than conformation (a) by approximately 7.28 kJ/mol (1.74 kcal/mol).

EXAMPLE 3.9

Label all axial–axial interactions in the following chair conformation:



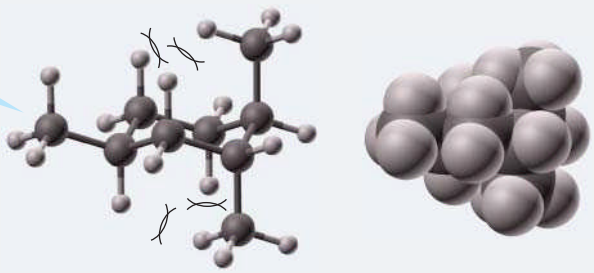
STRATEGY

Find each axial group. Those on the same side of the chair conformation (either above or below the ring) will participate in axial–axial interactions. Remember that the equatorial substituents do not participate in axial–axial interactions.

SOLUTION

There are four axial–axial interactions: Each axial methyl group has two sets of axial–axial interactions with parallel hydrogen atoms on the same side of the ring. The equatorial methyl group has no axial–axial interactions.

because equatorial groups do not have axial–axial interactions, it is energetically more favorable for a group to be equatorial rather than axial



See problem 3.38

PROBLEM 3.9

The conformational equilibria for methyl-, ethyl-, and isopropylcyclohexane are all about 95% in favor of the equatorial conformation, but the conformational equilibrium for *tert*-butylcyclohexane is almost completely on the equatorial side. Explain why the conformational equilibria for the first three compounds are comparable, but that for *tert*-butylcyclohexane lies considerably farther toward the equatorial conformation.

3.7 What Is *Cis–Trans* Isomerism in Cycloalkanes?

***Cis–trans* isomers** Isomers that have the same order of attachment of their atoms, but a different arrangement of their atoms in space, due to the presence of either a ring or a carbon–carbon double bond.

Trans A prefix meaning "across from."

Cis A prefix meaning "on the same side."

Cycloalkanes with substituents on two or more carbons of the ring show a type of isomerism called ***cis–trans* isomerism**. *Cis–trans* isomers have (1) the same molecular formula, (2) the same order of attachment of atoms, and (3) an arrangement of atoms that cannot be interchanged by rotation about sigma bonds under ordinary conditions. By way of comparison, the potential energy difference between conformations is so small that they can be interconverted easily at or near room temperature by rotation about single bonds, while *cis–trans* isomers can only be interconverted at extremely high temperatures or not at all.

We can illustrate *cis–trans* isomerism in cycloalkanes using 1,2-dimethylcyclopentane as an example. In the following structural formula, the cyclopentane ring is drawn as a planar pentagon viewed edge on (in determining the number of *cis–trans* isomers

Chemical Connections 3A

THE POISONOUS PUFFER FISH

Nature is by no means limited to carbon in six-membered rings. Tetrodotoxin, one of the most potent toxins known, is composed of a set of interconnected six-membered rings, each in a chair conformation. All but one of these rings have atoms other than carbon in them. Tetrodotoxin is produced in the liver and ovaries of many species of *Tetraodontidae*, especially the puffer fish, so called because it inflates itself to an almost spherical spiny ball when alarmed. The puffer is evidently a species that is highly preoccupied with defense, but the Japanese are not put off. They regard the puffer, called *fugu* in Japanese, as a delicacy. To serve it in a public restaurant, a chef must be registered as sufficiently skilled in removing the toxic organs so as to make the flesh safe to eat.

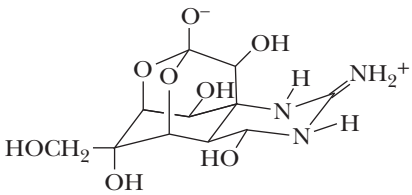
Symptoms of tetrodotoxin poisoning begin with attacks of severe weakness, progressing to complete paralysis and eventual death. Tetrodotoxin exerts its severe poisonous effect by blocking Na^+ ion channels in excitable membranes. The $=NH_2^+$ end of tetrodotoxin lodges in the mouth of a Na^+ ion channel, thus blocking further transport of Na^+ ions through the channel.

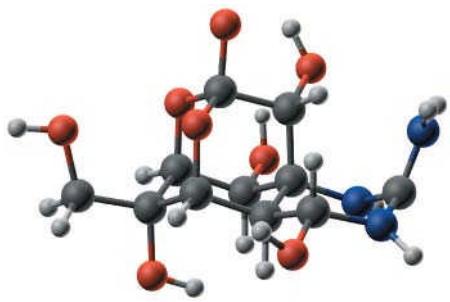
Greg Elms/Getty Images

A puffer fish inflated.

Questions

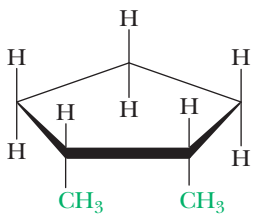
How many chair conformations are present in tetrodotoxin? Which substituents in tetrodotoxin are involved in axial–axial interactions?



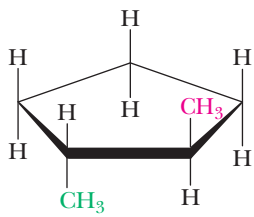


Tetrodotoxin

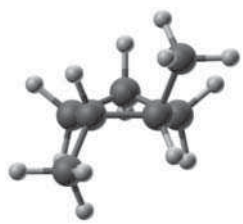
in a substituted cycloalkane, it is adequate to draw the cycloalkane ring as a planar polygon):



cis-1,2-Dimethylcyclopentane



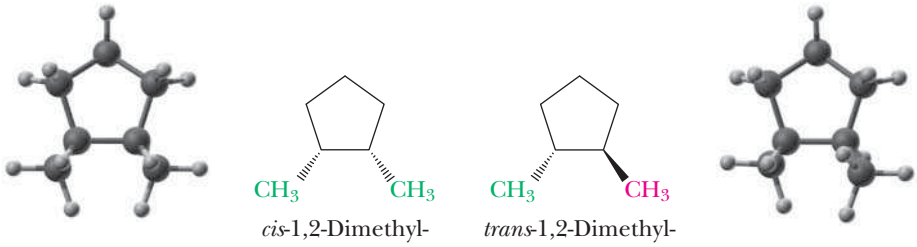
trans-1,2-Dimethylcyclopentane



Carbon–carbon bonds of the ring that project forward are shown as heavy lines. When viewed from this perspective, substituents bonded to the cyclopentane ring project above and below the plane of the ring. In one isomer of 1,2-dimethylcyclopentane, the methyl groups are on the same side of the ring (either both above or both below the plane of the ring); in the other isomer, they are on opposite sides of the ring (one above and one below the plane of the ring).

Alternatively, the cyclopentane ring can be viewed from above, with the ring in the plane of the paper. Substituents on the ring then either project toward you (that is, they project up above the page) and are shown by solid wedges, or they project away from you (they project

down below the page) and are shown by broken wedges. In the following structural formulas, only the two methyl groups are shown (hydrogen atoms of the ring are not shown):



cis-1,2-Dimethylcyclopentane

trans-1,2-Dimethylcyclopentane

Two *cis–trans* isomers exist for 1,4-dimethylcyclohexane. For the purposes of determining the number of *cis–trans* isomers in substituted cycloalkanes, it is adequate to draw the cycloalkane ring as a planar polygon, as is done in the following disubstituted cyclohexanes:

trans-1,4-Dimethylcyclohexane

cis-1,4-Dimethylcyclohexane

We can also draw the *cis* and *trans* isomers of 1,4-dimethylcyclohexane as nonplanar chair conformations. In working with alternative chair conformations, it is helpful to remember that all groups axial on one chair are equatorial in the alternative chair, and vice versa. In

EXAMPLE 3.10

Which cycloalkanes show *cis–trans* isomerism? For each that does, draw both isomers.

(a) Methylcyclopentane **(b)** 1,1-Dimethylcyclobutane **(c)** 1,3-Dimethylcyclobutane

STRATEGY

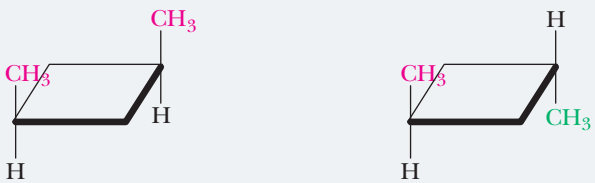
In order to exhibit *cis–trans* isomerism, a cyclic compound must have at least two substituents on the ring and there must be two possible arrangements (*cis* and *trans*) for any pair of substituents.

SOLUTION

(a) Methylcyclopentane does not show *cis–trans* isomerism: It has only one substituent on the ring.

(b) 1,1-Dimethylcyclobutane does not show *cis–trans* isomerism: Only one arrangement is possible for the two methyl groups on the ring, and they must be *trans*.

(c) 1,3-Dimethylcyclobutane shows *cis–trans* isomerism. Note that, in these structural formulas, we show only the hydrogens on carbons bearing the methyl groups.



cis-1,3-Dimethylcyclobutane

trans-1,3-Dimethylcyclobutane

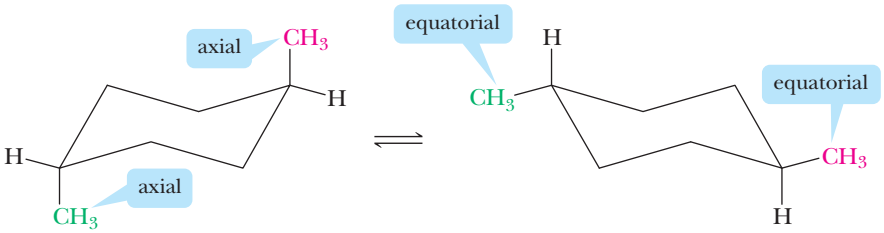
See problems 3.41–3.44, 3.46

PROBLEM 3.10

Which cycloalkanes show *cis–trans* isomerism? For each that does, draw both isomers.

(a) 1,3-Dimethylcyclopentane **(b)** Ethylcyclopentane **(c)** 1-Ethyl-2-methylcyclobutane

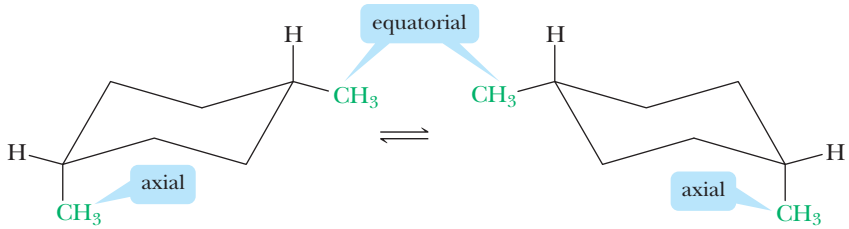
one chair conformation of *trans*-1,4-dimethylcyclohexane, the two methyl groups are axial; in the alternative chair conformation, they are equatorial. Of these chair conformations, the one with both methyls equatorial is considerably more stable.



(less stable) (more stable)

trans-1,4-Dimethylcyclohexane

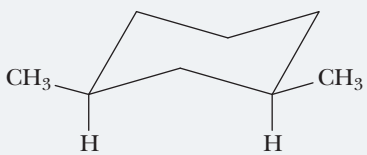
The alternative chair conformations of *cis*-1,4-dimethylcyclohexane are of equal energy. In each chair conformation, one methyl group is equatorial and the other is axial.



cis-1,4-Dimethylcyclohexane
(these conformations are of equal stability)

EXAMPLE 3.11

Following is a chair conformation of 1,3-dimethylcyclohexane:



(a) Is this a chair conformation of *cis*-1,3-dimethylcyclohexane or of *trans*-1,3-dimethylcyclohexane?
(b) Draw the alternative chair conformation. Of the two chair conformations, which is the more stable?
(c) Draw a planar hexagon representation of the isomer shown in this example.

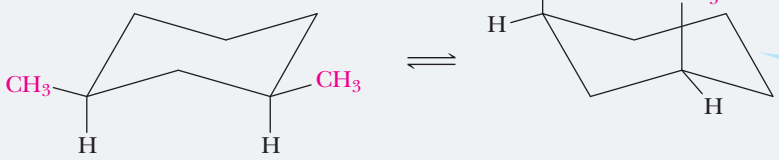
STRATEGY

Determine whether substituents are on the same or different sides of the ring to determine *cis* or *trans*. To perform a chair-to-chair interconversion, change the orientation of the rightmost and leftmost carbons in the chair conformation of cyclohexane. Remember that after such an interconversion, all prior axial substituents become equatorial and all prior equatorial substituents become axial. When converting to planar representations of cyclohexane, show substituents above the ring as coming out of the page (wedges) and those below the ring as going behind the page (dashes).

SOLUTION

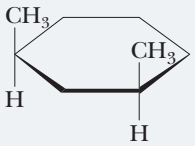
(a) The isomer shown is *cis*-1,3-dimethylcyclohexane; the two methyl groups are on the same side of the ring.

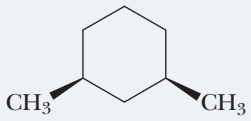
(b)



(more stable) (less stable)

a chair-to-chair interconversion will *never* change the *cis* or *trans* relationship between two substituents. That is, *cis* will remain *cis* and *trans* will remain *trans*

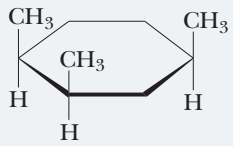
(c) 

or 

See problems 3.41–3.44, 3.46, 3.47

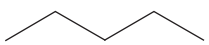
PROBLEM 3.11

Following is a planar hexagon representation of one isomer of 1,2,4-trimethylcyclohexane. Draw the alternative chair conformations of this compound, and state which is the more stable.

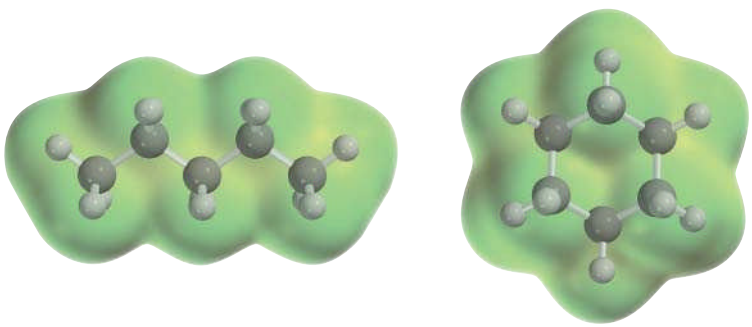


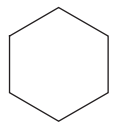
3.8 What Are the Physical Properties of Alkanes and Cycloalkanes?

The most important property of alkanes and cycloalkanes is their almost complete lack of polarity. As we saw in Section 1.2C, the difference in electronegativity between carbon and hydrogen is 2.5 − 2.1 = 0.4 on the Pauling scale, and given this small difference, we classify a C—H bond as nonpolar covalent. Therefore, alkanes are nonpolar compounds, and there are only weak interactions between their molecules.



Pentane





Cyclohexane

Pentane and cyclohexane. The electron density models show no evidence of any polarity in alkanes and cycloalkanes.

A. Boiling Points

The boiling points of alkanes are lower than those of almost any other type of compound with the same molecular weight. In general, both boiling and melting points of alkanes increase with increasing molecular weight (Table 3.4).

Alkanes containing 1 to 4 carbons are gases at room temperature, and those containing 5 to 17 carbons are colorless liquids. High-molecular-weight alkanes (those with 18 or more carbons) are white, waxy solids. Several plant waxes are high-molecular-weight alkanes. The wax found in apple skins, for example, is an unbranched alkane with the molecular formula $C_{27}H_{56}$. Paraffin wax, a mixture of high-molecular-weight alkanes, is used for wax candles, in lubricants, and to seal home-canned jams, jellies, and other preserves. Petrolatum, so named because it is derived from petroleum refining, is a liquid

TABLE 3.4 Physical Properties of Some Unbranched Alkanes

Name	Condensed Structural Formula	Melting Point (°C)	Boiling Point (°C)	*Density of Liquid (g/mL at 0 °C)
methane	CH_4	–182	–164	(a gas)
ethane	CH_3CH_3	–183	–88	(a gas)
propane	$CH_3CH_2CH_3$	–190	–42	(a gas)
butane	$CH_3(CH_2)_2CH_3$	–138	0	(a gas)
pentane	$CH_3(CH_2)_3CH_3$	–130	36	0.626
hexane	$CH_3(CH_2)_4CH_3$	–95	69	0.659
heptane	$CH_3(CH_2)_5CH_3$	–90	98	0.684
octane	$CH_3(CH_2)_6CH_3$	–57	126	0.703
nonane	$CH_3(CH_2)_7CH_3$	–51	151	0.718
decane	$CH_3(CH_2)_8CH_3$	–30	174	0.730

*For comparison, the density of H_2O is 1 g/mL at 4 °C.

mixture of high-molecular-weight alkanes. Sold as mineral oil and Vaseline, petrolatum is used as an ointment base in pharmaceuticals and cosmetics and as a lubricant and rust preventative.

B. Dispersion Forces and Interactions between Alkane Molecules

Methane is a gas at room temperature and atmospheric pressure. It can be converted to a liquid if cooled to –164 °C and to a solid if further cooled to –182 °C. The fact that methane (or any other compound, for that matter) can exist as a liquid or a solid depends on the existence of forces of attraction between particles of the pure compound. Although the forces of attraction between particles are all electrostatic in nature, they vary widely in their relative strengths. The strongest attractive forces are between ions—for example, between Na^+ and Cl^- in NaCl (787 kJ/mol, 188 kcal/mol). Hydrogen bonding is a weaker attractive force (8–42 kJ/mol, 2–10 kcal/mol). We will have more to say about hydrogen bonding in Chapter 8 when we discuss the physical properties of alcohols—compounds containing polar O—H groups.

Dispersion forces (0.08–8 kJ/mol, 0.02–2 kcal/mol) are the weakest intermolecular attractive forces. It is the existence of dispersion forces that accounts for the fact that low-molecular-weight, nonpolar substances such as methane can be liquefied. When we convert methane from a liquid to a gas at –164°C, for example, the process of separating its molecules requires only enough energy to overcome the very weak dispersion forces.

To visualize the origin of dispersion forces, it is necessary to think in terms of instantaneous distributions of electron density rather than average distributions. Over time, the distribution of electron density in a methane molecule is symmetrical [Figure 3.12(a)],

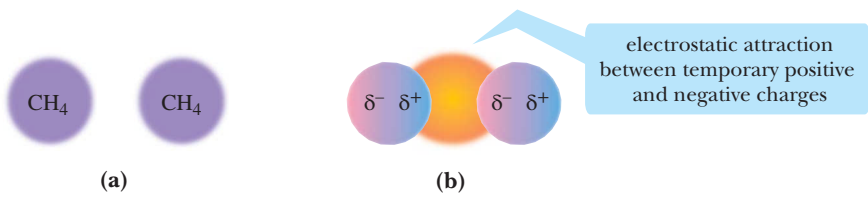


FIGURE 3.12 Dispersion forces. (a) The average distribution of electron density in a methane molecule is symmetrical, and there is no polarity. (b) Temporary polarization of one molecule induces temporary polarization in an adjacent molecule. Electrostatic attractions between temporary partial positive and partial negative charges are called *dispersion forces*.

Dispersion forces Very weak intermolecular forces of attraction resulting from the interaction of temporary induced dipoles.

and there is no separation of charge. However, at any instant, there is a nonzero probability that the electron density is polarized (shifted) more toward one part of a methane molecule than toward another. This temporary polarization creates temporary partial positive and partial negative charges, which in turn induce temporary partial positive and negative charges in adjacent methane molecules [Figure 3.12(b)]. **Dispersion forces** are weak electrostatic attractive forces that occur between temporary partial positive and partial negative charges in adjacent atoms or molecules.

Because interactions between alkane molecules consist only of these very weak dispersion forces, the boiling points of alkanes are lower than those of almost any other type of compound with the same molecular weight. As the number of atoms and the molecular weight of an alkane increase, the strength of the dispersion forces among alkane molecules increases, and consequently, boiling points increase.

C. Melting Point and Density

The melting points of alkanes increase with increasing molecular weight. The increase, however, is not as regular as that observed for boiling points, because the ability of molecules to pack into ordered patterns of solids changes as the molecular size and shape change.

The average density of the alkanes listed in Table 3.4 is about 0.7 g/mL; that of higher-molecular-weight alkanes is about 0.8 g/mL. All liquid and solid alkanes are less dense than water (1.0 g/mL); therefore, they float on water.

D. Constitutional Isomers Have Different Physical Properties

Alkanes that are constitutional isomers are different compounds and have different physical properties. Table 3.5 lists the boiling points, melting points, and densities of the five constitutional isomers with the molecular formula C_6H_{14}. The boiling point of each of its branched-chain isomers is lower than that of hexane itself, and the more branching there is, the lower is the boiling point. These differences in boiling points are related to molecular shape in the following way: The only forces of attraction between alkane molecules are dispersion forces. As branching increases, the shape of an alkane molecule becomes more compact, and its surface area decreases. As the surface area decreases, the strength of the dispersion forces decreases, and boiling points decrease. Thus, for any group of alkane constitutional isomers, it is usually observed that the least-branched isomer has the highest boiling point and the most-branched isomer has the lowest boiling point. The trend in melting points is less obvious, but as previously mentioned, it correlates with a molecule's ability to pack into ordered patterns of solids.

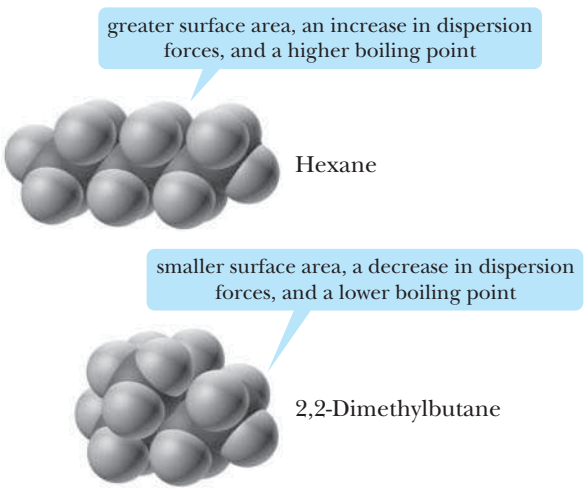


TABLE 3.5 Physical Properties of the Isomeric Alkanes with the Molecular Formula C_6H_{14}

Name	Melting Point (°C)	Boiling Point (°C)	Density (g/mL)
hexane	−95	69	0.659
3-methylpentane	−118	64	0.664
2-methylpentane	−154	62	0.653
2,3-dimethylbutane	−129	58	0.662
2,2-dimethylbutane	−100	50	0.649

EXAMPLE 3.12

Arrange the alkanes in each set in order of increasing boiling point:

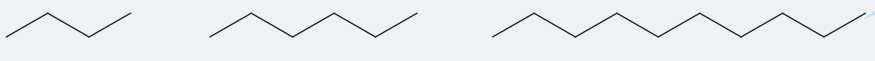
(a) Butane, decane, and hexane **(b)** 2-Methylheptane, octane, and 2,2,4-trimethylpentane

STRATEGY

When determining relative boiling points, remember that as the number of carbon atoms in the chain increases, the dispersion forces among molecules increase and the boiling points increase. Boiling point is also dependent on the degree of branching. For constitutional isomers, the most highly branched isomer has the smallest surface area and the lowest boiling point.

SOLUTION

(a) All of the compounds are unbranched alkanes. As the number of carbon atoms in the chain increases, the dispersion forces among molecules increase, and the boiling points increase. Decane has the highest boiling point, butane the lowest:

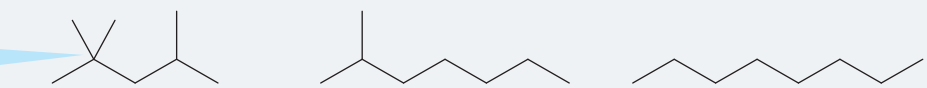


Butane (bp −0.5 °C) Hexane (bp 69 °C) Decane (bp 174 °C)

in unbranched hydrocarbons, the longer the chain length, the higher is the surface area. This results in an increase in the dispersion forces and an increase in boiling point

(b) These three alkanes are constitutional isomers with the molecular formula C_8H_{18}. Their relative boiling points depend on the degree of branching. 2,2,4-Trimethylpentane, the most highly branched isomer, has the smallest surface area and the lowest boiling point. Octane, the unbranched isomer, has the largest surface area and the highest boiling point.

the greater the branching, the lower is the surface area, causing a decrease in the dispersion forces and a decrease in boiling point



2,2,4-Trimethylpentane (bp 99 °C) 2-Methylheptane (bp 118 °C) Octane (bp 125 °C)

See problem 3.49

PROBLEM 3.12

Arrange the alkanes in each set in order of increasing boiling point:

(a) 2-Methylbutane, 2,2-dimethylpropane, and pentane **(b)** 3,3-Dimethylheptane, 2,2,4-trimethylhexane, and nonane

3.9 What Are the Characteristic Reactions of Alkanes?

The most important chemical property of alkanes and cycloalkanes is their inertness. They are quite unreactive toward most reagents, a behavior consistent with the fact that they are nonpolar compounds containing only strong sigma bonds. Under certain conditions, however, alkanes and cycloalkanes do react with oxygen, O_2. By far their most important reaction with oxygen is oxidation (combustion) to form carbon dioxide and water. The oxidation of saturated hydrocarbons is the basis for their use as energy sources for heat [natural gas, liquefied petroleum gas (LPG), and fuel oil] and power (gasoline, diesel fuel, and aviation fuel). Following are balanced equations for the complete combustion

of methane, the major component of natural gas, and for propane, the major component of LPG:

when balancing equations for combustion reactions of hydrocarbons, first balance the number of carbons, next balance the number of hydrogens, then balance the number of oxygens. If the equation is still not balanced, consider doubling all coefficients on each side of the equation arrow

$$\underset{\text{Methane}}{CH_4} + 2O_2 \longrightarrow CO_2 + 2H_2O \quad \Delta H^\circ = -886 \text{ kJ/mol}(-212 \text{ kcal/mol})$$

$$\underset{\text{Propane}}{CH_3CH_2CH_3} + 5O_2 \longrightarrow 3CO_2 + 4H_2O \quad \Delta H^\circ = -2{,}220 \text{ kJ/mol}(-530 \text{ kcal/mol})$$

3.10 What Are the Sources of Alkanes?

The three major sources of alkanes throughout the world are the fossil fuels: natural gas, petroleum, and coal. Fossil fuels account for approximately 90% of the total energy consumed in the United States. Nuclear electric power and hydroelectric power make up most of the remaining 10%. In addition, fossil fuels provide the bulk of the raw material for the organic chemicals consumed worldwide.

A. Natural Gas

Natural gas consists of approximately 90–95% methane, 5–10% ethane, and a mixture of other relatively low-boiling alkanes—chiefly propane, butane, and 2-methylpropane. The current widespread use of ethylene as the organic chemical industry's most important building block is largely the result of the ease with which ethane can be separated from natural gas and cracked into ethylene. Cracking is a process whereby a saturated hydrocarbon is converted into an unsaturated hydrocarbon plus H_2. Heating it in a furnace at 800 to 900°C for a fraction of a second cracks ethane. The global production of ethylene in 2013 was 155 billion kg (342 billion pounds), making it the number-one organic compound produced, on a weight basis. The bulk of the ethylene produced is used to create organic polymers, as described in Chapter 16.

$$\underset{\text{Ethane}}{CH_3CH_3} \xrightarrow[\text{(thermal cracking)}]{800\text{–}900^\circ C} \underset{\text{Ethylene}}{CH_2{=}CH_2} + H_2$$

B. Petroleum

Petroleum is a thick, viscous liquid mixture of literally thousands of compounds, most of them hydrocarbons, formed from the decomposition of marine plants and animals. Petroleum and petroleum-derived products fuel automobiles, aircraft, and trains. They provide most of the greases and lubricants required for the machinery of our highly industrialized society. Furthermore, petroleum, along with natural gas, provides close to 90% of the organic raw materials used in the synthesis and manufacture of synthetic fibers, plastics, detergents, drugs, dyes, and a multitude of other products.

It is the task of a petroleum refinery to produce usable products, with a minimum of waste, from the thousands of different hydrocarbons in this liquid mixture. The various physical and chemical processes for this purpose fall into two broad categories: separation processes, which separate the complex mixture into various fractions, and re-forming processes, which alter the molecular structure of the hydrocarbon components themselves.

The fundamental separation process utilized in refining petroleum is fractional distillation (Figure 3.13). Practically all crude oil that enters a refinery goes to distillation units, where it is heated to temperatures as high as 370 to 425°C and separated into fractions. Each fraction contains a mixture of hydrocarbons that boils within a particular range:

A petroleum refinery.

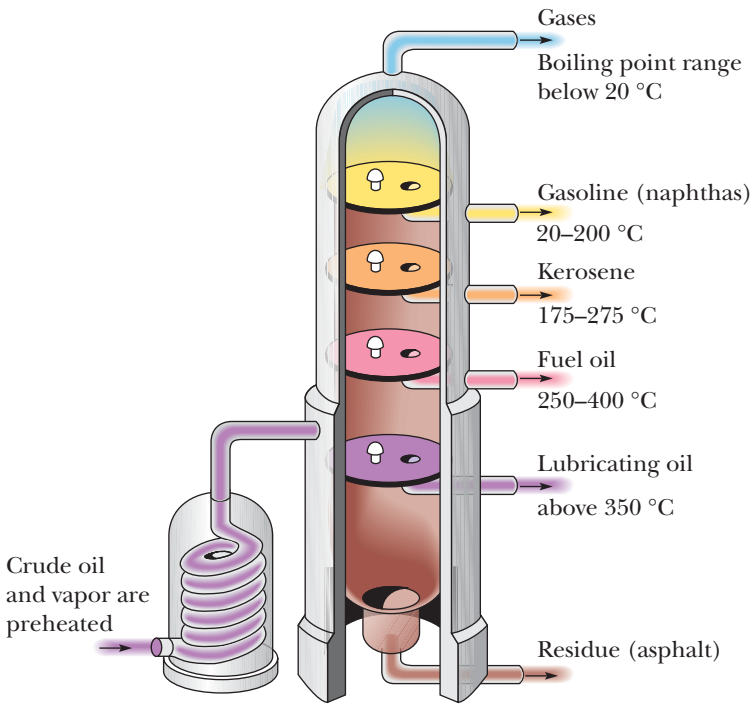
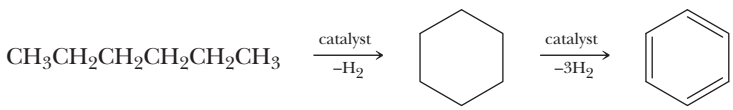


FIGURE 3.13 Fractional distillation of petroleum. The lighter, more volatile fractions are removed from higher up the column and the heavier, less volatile fractions from lower down.

1. Gases boiling below 20°C are taken off at the top of the distillation column. This fraction is a mixture of low-molecular-weight hydrocarbons, predominantly propane, butane, and 2-methylpropane, substances that can be liquefied under pressure at room temperature. The liquefied mixture, known as liquefied petroleum gas (LPG), can be stored and shipped in metal tanks and is a convenient source of gaseous fuel for home heating and cooking.
2. Naphthas, bp 20 to 200 °C, are a mixture of C_5 to C_{12} alkanes and cycloalkanes. Naphthas also contain small amounts of benzene, toluene, xylene, and other aromatic hydrocarbons (Chapter 9). The light naphtha fraction, bp 20 to 150 °C, is the source of straight-run gasoline and averages approximately 25% of crude petroleum. In a sense, naphthas are the most valuable distillation fractions, because they are useful not only as fuel, but also as sources of raw materials for the organic chemical industry.
3. Kerosene, bp 175 to 275°C, is a mixture of C_9 to C_{15} hydrocarbons.
4. Fuel oil, bp 250 to 400°C, is a mixture of C_{15} to C_{18} hydrocarbons. Diesel fuel is obtained from this fraction.
5. Lubricating oil and heavy fuel oil distill from the column at temperatures above 350 °C.
6. Asphalt is the black, tarry residue remaining after the removal of the other volatile fractions.

The two most common re-forming processes are cracking, illustrated by the thermal conversion of ethane to ethylene (Section 3.10A), and catalytic re-forming, illustrated by the conversion of hexane first to cyclohexane and then to benzene:



Hexane Cyclohexane Benzene

C. Coal

To understand how coal can be used as a raw material for the production of organic compounds, it is necessary to discuss synthesis gas. Synthesis gas is a mixture of carbon monoxide and hydrogen in varying proportions, depending on the means by which it is manufactured. Synthesis gas is prepared by passing steam over coal. It is also prepared by the partial oxidation of methane by oxygen.

$$\underset{\text{Coal}}{C} + H_2O \xrightarrow{\text{heat}} CO + H_2$$

$$\underset{\text{Methane}}{CH_4} + \frac{1}{2}O_2 \xrightarrow{\text{catalyst}} CO + 2H_2$$

Two important organic compounds produced today almost exclusively from carbon monoxide and hydrogen are methanol and acetic acid. In the production of methanol, the ratio of carbon monoxide to hydrogen is adjusted to 1:2, and the mixture is passed over a catalyst at elevated temperature and pressure:

$$CO + 2H_2 \xrightarrow{\text{catalyst}} \underset{\text{Methanol}}{CH_3OH}$$

The treatment of methanol, in turn, with carbon monoxide over a different catalyst gives acetic acid:

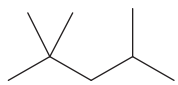
$$\underset{\text{Methanol}}{CH_3OH} + CO \xrightarrow{\text{catalyst}} \underset{\text{Acetic acid}}{CH_3\overset{\overset{O}{\|}}{C}OH}$$

Because the processes for making methanol and acetic acid directly from carbon monoxide are commercially proven, it is likely that the decades ahead will see the development of routes to other organic chemicals from coal via methanol.

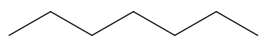
Chemical Connections 3B

OCTANE RATING: WHAT THOSE NUMBERS AT THE PUMP MEAN

Gasoline is a complex mixture of C_6 to C_{12} hydrocarbons. The quality of gasoline as a fuel for internal combustion engines is expressed in terms of an *octane rating*. Engine knocking occurs when a portion of the air–fuel mixture explodes prematurely (usually as a result of heat developed during compression) and independently of ignition by the spark plug. Two compounds were selected as reference fuels. One of these, 2,2,4-trimethylpentane (isooctane), has very good antiknock properties (the fuel–air mixture burns smoothly in the combustion chamber) and was assigned an octane rating of 100. (The name *isooctane* is a trivial name; its only relation to the name 2,2,4-trimethylpentane is that both names show eight carbon atoms.) Heptane, the other reference compound, has poor antiknock properties and was assigned an octane rating of 0.



2,2,4-Trimethylpentane
(octane rating 100)



Heptane
(octane rating 0)

The octane rating of a particular gasoline is that percentage of isooctane in a mixture of isooctane and heptane that has antiknock properties equivalent to those of the gasoline. For example, the antiknock properties of 2-methylhexane are the same as those of a mixture of 42% isooctane and 58% heptane; therefore, the octane rating of 2-methylhexane is 42. Octane itself has an octane rating of –20, which means that it produces even more engine knocking than heptane. Ethanol, the additive to gasohol, has an octane rating of 105. Benzene and toluene have octane ratings of 106 and 120, respectively.

Charles D. Winters

Typical octane ratings of commonly available gasolines.

Question

Which would you expect to have a higher boiling point, octane or isooctane (2,2,4-trimethylpentane)?

SUMMARY OF KEY QUESTIONS

3.1 What Are Alkanes?

- A **hydrocarbon** is a compound that contains only carbon and hydrogen. An alkane is a **saturated hydrocarbon** and contains only single bonds. **Alkanes** have the general formula C_nH_{2n+2}.

3.2 What Is Constitutional Isomerism in Alkanes?

- **Constitutional isomers** have the same molecular formula but a different connectivity (a different order of attachment) of their atoms.

3.3 How Do We Name Alkanes?

- Alkanes are named according to a set of rules developed by the **International Union of Pure and Applied Chemistry (IUPAC)**.
- A carbon atom is classified as **primary (1°)**, **secondary (2°)**, **tertiary (3°)**, or **quaternary (4°)**, depending on the number of carbon atoms bonded to it.
- A hydrogen atom is classified as **primary (1°)**, **secondary (2°)**, or **tertiary (3°)**, depending on the type of carbon to which it is bonded.

3.4 What Are Cycloalkanes?

- A **cycloalkane** is an alkane that contains carbon atoms bonded to form a ring.
- To name a cycloalkane, prefix the name of the open-chain hydrocarbon with "cyclo."
- Five-membered rings (cyclopentanes) and six-membered rings (cyclohexanes) are especially abundant in the biological world.

3.5 What Is the IUPAC System of Nomenclature?

- The IUPAC system is a general system of **nomenclature**. The IUPAC name of a compound consists of three parts:
  (1) A **prefix** that indicates the number of carbon atoms in the **parent chain**,
  (2) An **infix** that indicates the nature of the carbon–carbon bonds in the parent chain, and
  (3) A **suffix** that indicates the class to which the compound belongs.
  (4) **Substituents** derived from alkanes by the removal of a hydrogen atom are called **alkyl groups** and are given the symbol **R**. The name of an alkyl group is formed by dropping the suffix -ane from the name of the parent alkane and adding -yl in its place.

3.6 What Are the Conformations of Alkanes and Cycloalkanes?

- A **conformation** is any three-dimensional arrangement of the atoms of a molecule that results from rotation about a single bond.
- One convention for showing conformations is the **Newman projection**. **Staggered conformations** are lower in energy (more stable) than **eclipsed conformations**.
- There are three types of **molecular strain**:

  Torsional strain (also called **eclipsed interaction strain**) that results when nonbonded atoms separated by three bonds are forced from a staggered conformation to an eclipsed conformation

  Angle strain that results when a bond angle in a molecule is either expanded or compressed compared with its optimal values, and

  Steric strain (also called **nonbonded interaction strain**) that results when nonbonded atoms separated by four or more bonds are forced abnormally close to each other—that is, when they are forced closer than their **atomic (contact) radii** would otherwise allow.
- Cyclopentanes, cyclohexanes, and all larger cycloalkanes exist in dynamic equilibrium between a set of **puckered conformations**. The lowest energy conformation of cyclopentane is an **envelope conformation**. The lowest energy conformations of cyclohexane are two interconvertible **chair conformations**. In a chair conformation, six bonds are **axial** and six are **equatorial**. Bonds axial in one chair are equatorial in the alternative chair, and vice versa. A **boat conformation** is higher in energy than chair conformations. The more stable conformation of a substituted cyclohexane is the one that minimizes **axial–axial interactions**.

3.7 What Is *Cis–Trans* Isomerism in Cycloalkanes?

- ***Cis–trans* isomers** have the same molecular formula and the same order of attachment of atoms, but arrangements of atoms in space that cannot be interconverted by rotation about single bonds. ***Cis*** means that substituents are on the same side of the ring; ***trans*** means that they are on opposite sides of the ring. Most cycloalkanes with substituents on two or more carbons of the ring show *cis–trans* isomerism.

3.8 What Are the Physical Properties of Alkanes and Cycloalkanes?

- Alkanes are **nonpolar compounds**, and the only forces of attraction between their molecules are **dispersion forces**,

which are weak electrostatic interactions between temporary partial positive and negative charges of atoms or molecules. Low-molecular-weight alkanes, such as methane, ethane, and propane, are gases at room temperature and atmospheric pressure.

- Higher-molecular-weight alkanes, such as those in gasoline and **kerosene**, are liquids.
- Very high-molecular-weight alkanes, such as those in **paraffin wax**, are solids.
- Among a set of alkane constitutional isomers, the least branched isomer generally has the highest boiling point; the most branched isomer generally has the lowest boiling point.

3.9 What Are the Characteristic Reactions of Alkanes?

- The most important chemical property of alkanes and cycloalkanes is their inertness. Because they are nonpolar compounds containing only strong sigma bonds, they are quite unreactive toward most reagents.
- By far, their most important reaction is **combustion** to form carbon dioxide and water. The oxidation of saturated hydrocarbons is the basis for their use as energy sources for heat and power.

3.10 What Are the Sources of Alkanes?

- **Natural gas** consists of 90–95% methane with lesser amounts of ethane and other lower-molecular-weight hydrocarbons.
- **Petroleum** is a liquid mixture of literally thousands of different hydrocarbons.
- **Synthesis gas**, a mixture of carbon monoxide and hydrogen, can be derived from natural gas and coal.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Combustion of alkanes is an endothermic process. (3.9)
2. All alkanes that are liquid at room temperature are more dense than water. (3.8)
3. The two main sources of alkanes the world over are petroleum and natural gas. (3.10)
4. There are four alkyl groups with the molecular formula C_4H_9. (3.3)
5. Sets of constitutional isomers have the same molecular formula and the same physical properties. (3.2)
6. A hydrocarbon is composed of only carbon and hydrogen. (3.1)
7. Cycloalkanes are saturated hydrocarbons. (3.4)
8. The products of complete combustion of an alkane are carbon dioxide and water. (3.9)
9. Alkanes and cycloalkanes show *cis–trans* isomerism. (3.6)
10. Alkenes and alkynes are unsaturated hydrocarbons. (3.1)
11. There are two constitutional isomers with the molecular formula C_4H_{10}. (3.2)
12. Hexane and cyclohexane are constitutional isomers. (3.4)
13. The propyl and isopropyl groups are constitutional isomers. (3.3)
14. There are five constitutional isomers with the molecular formula C_5H_{12}. (3.2)
15. Boiling points among alkanes with unbranched carbon chains increase as the number of carbons in the chain increases. (3.8)
16. In a cyclohexane ring, if an axial bond is above the plane of the ring on a particular carbon atom, axial bonds on the two adjacent carbons are below the plane of the ring. (3.5)
17. Fractional distillation of petroleum separates hydrocarbons based on their melting points (3.10)
18. Among alkane constitutional isomers, the least branched isomer generally has the lowest boiling point. (3.8)
19. The parent name of a cycloalkane is the name of the unbranched alkane with the same number of carbon atoms as are in the cycloalkane ring. (3.4)
20. Octane and 2,2,4-trimethylpentane are constitutional isomers and have the same octane number. (3.10)
21. Liquid alkanes and cycloalkanes are soluble in each other. (3.8)
22. Alkanes and cycloalkanes are insoluble in water. (3.8)
23. The more stable chair conformation of a substituted cyclohexane has the greater number of substituents in equatorial positions. (3.5)
24. The parent name of an alkane is the name of the longest chain of carbon atoms. (3.3)
25. Alkanes are saturated hydrocarbons. (3.1)
26. The general formula of an alkane is C_nH_{2n}, where n is the number of carbon atoms in the alkane. (3.1)
27. The octane number of a particular gasoline is the number of grams of octane per liter. (3.10)
28. *Cis* and *trans* isomers have the same molecular formula, the same connectivity, and the same physical properties. (3.8)
29. A *cis* isomer of a disubstituted cycloalkane can be converted to a *trans* isomer by rotation about an appropriate carbon–carbon single bond. (3.6)
30. All cycloalkanes with two substituents on the ring show *cis–trans* isomerism. (3.6)

31. In all conformations of ethane, propane, butane, and higher alkanes, all C—C—C and C—C—H bond angles are approximately 109.5°. (3.5)

32. Conformations have the same molecular formula and the same connectivity, but differ in the three-dimensional arrangement of their atoms in space. (3.5)

33. Constitutional isomers have the same molecular formula and the same connectivity of their atoms. (3.2)

Answers: (1) F (2) F (3) T (4) T (5) F (6) T (7) T (8) T (9) F (10) T (11) T (12) F (13) T (14) F (15) T (16) T (17) F (18) F (19) T (20) F (21) T (22) T (23) T (24) T (25) T (26) F (27) F (28) F (29) F (30) F (31) T (32) T (33) F

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

KEY REACTIONS

1. Oxidation of Alkanes (Section 3.9)

The oxidation of alkanes to carbon dioxide and water is the basis for their use as energy sources of heat and power:

$$CH_3CH_2CH_3 + 5O_2 \longrightarrow 3CO_2 + 4H_2O + \text{energy}$$

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 3.1 Structure of Alkanes

3.13 For each condensed structural formula, write a line-angle formula:

(a) $CH_3CH_2CH(CH_2CH_3)CH_2CH(CH_3)CH(CH_3)_2$

(b) $CH_3C(CH_3)_2CH_3$

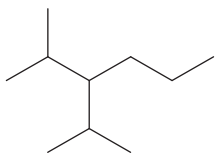
(c) $(CH_3)_2CHCH(CH_3)_2$

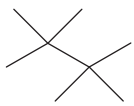
(d) $CH_3CH_2C(CH_2CH_3)_2CH_2CH_3$

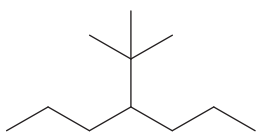
(e) $(CH_3)_3CH$

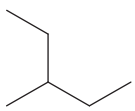
(f) $CH_3(CH_2)_3CH(CH_3)_2$

3.14 Write a condensed structural formula and the molecular formula of each alkane:

(a) 

(b) 

(c) 

(d) 

3.15 For each of the following condensed structural formulas, provide an even more abbreviated formula, using parentheses and subscripts:

(a) $CH_3CH_2CH_2CH_2CH_2CH(CH_3)CH_3$

(b) $HC(CH_2CH_2CH_3)_2CH_2CH_2CH_3$

(c) $CH_3C(CH_2CH_2CH_3)_2CH_2CH_2CH_2CH_2CH_3$

(d) $CH_3CH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_3$

SECTION 3.2 Constitutional Isomerism

3.16 Which statements are true about constitutional isomers?

(a) They have the same molecular formula.

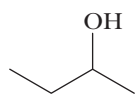
(b) They have the same molecular weight.

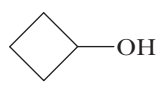
(c) They have the same order of attachment of atoms.

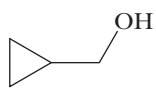
(d) They have the same physical properties.

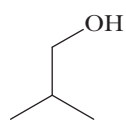
(e) Conformations are not constitutional isomers.

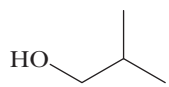
3.17 Each member of the following set of compounds is an alcohol; that is, each contains an —OH (hydroxyl group, Section 1.7A): **(See Example 3.1)**

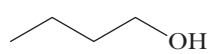
(a) 

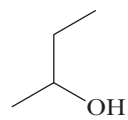
(b) 

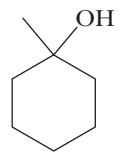
(c) 

(d) 

(e) 

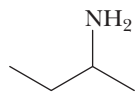
(f) 

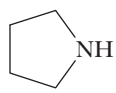
(g) 

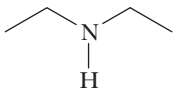
(h) 

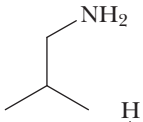
Which structural formulas represent (1) the same compound, (2) different compounds that are constitutional isomers, or (3) different compounds that are not constitutional isomers?

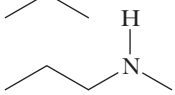
3.18 Each member of the following set of compounds is an amine; that is, each contains a nitrogen atom bonded to one, two, or three carbon groups (Section 1.7B): **(See Example 3.1)**

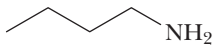
(a) 

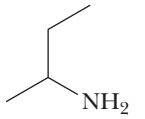
(b) 

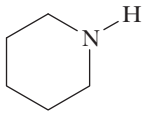
(c) 

(d) 

(e) 

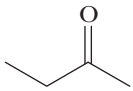
(f) 

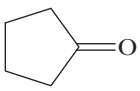
(g) 

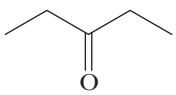
(h) 

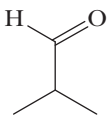
Which structural formulas represent (1) the same compound, (2) different compounds that are constitutional isomers, or (3) different compounds that are not constitutional isomers?

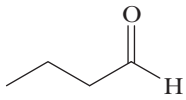
3.19 Each member of the following set of compounds is either an aldehyde or a ketone (Section 1.7C): **(See Example 3.1)**

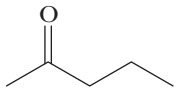
(a) 

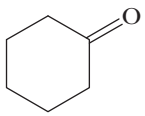
(b) 

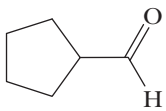
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

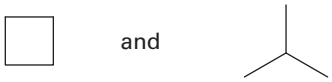
Which structural formulas represent (1) the same compound, (2) different compounds that are constitutional isomers, or (3) different compounds that are not constitutional isomers?

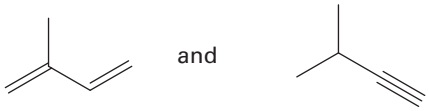
3.20 For each pair of compounds, tell whether the structural formulas shown represent **(See Example 3.1)**

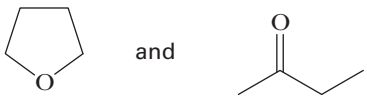
(1) the same compound,

(2) different compounds that are constitutional isomers, or

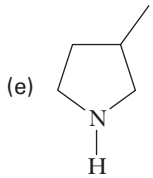
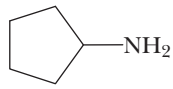
(3) different compounds that are not constitutional isomers:

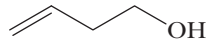
(a) 

(b) 

(c) 

(d) 

(e)  and 

(f)  and 

3.21 Name and draw line-angle formulas for the nine constitutional isomers with the molecular formula C_7H_{16}. **(See Example 3.2)**

3.22 Tell whether the compounds in each set are constitutional isomers: **(See Example 3.1)**

(a) CH_3CH_2OH and CH_3OCH_3

(b) $CH_3\overset{\overset{O}{\|}}{C}CH_3$ and $CH_3CH_2\overset{\overset{O}{\|}}{C}H$

(c) $CH_3\overset{\overset{O}{\|}}{C}OCH_3$ and $CH_3CH_2\overset{\overset{O}{\|}}{C}OH$

(d) $CH_3\overset{\overset{OH}{|}}{C}HCH_2CH_3$ and $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_3$

(e)  and $CH_3CH_2CH_2CH_2CH_3$

(f)  and $CH_2{=}CHCH_2CH_2CH_3$

3.23 Draw line-angle formulas for **(See Example 3.2)**

(a) The four alcohols with the molecular formula $C_4H_{10}O$.

(b) The two aldehydes with the molecular formula C_4H_8O.

(c) The one ketone with the molecular formula C_4H_8O.

(d) The three ketones with the molecular formula $C_5H_{10}O$.

(e) The four carboxylic acids with the molecular formula $C_5H_{10}O_2$.

(f) The four amines with the molecular formula C_3H_9N.

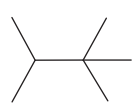
SECTIONS 3.3–3.5 Nomenclature of Alkanes and Cycloalkanes

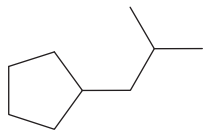
3.24 Write IUPAC names for these alkanes and cycloalkanes: **(See Examples 3.3, 3.5)**

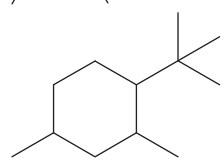
(a) $CH_3\underset{\underset{CH_3}{|}}{C}HCH_2CH_2CH_3$

(b) $CH_3\underset{\underset{CH_3}{|}}{C}HCH_2CH_2\underset{\underset{CH_3}{|}}{C}HCH_3$

(c) $CH_3(CH_2)_4\underset{\underset{CH_2CH_3}{|}}{C}HCH_2CH_3$

(d) 

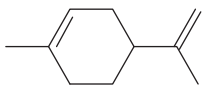
(e) 

(f) 

3.25 Write line-angle formulas for these alkanes: **(See Examples 3.3, 3.5)**

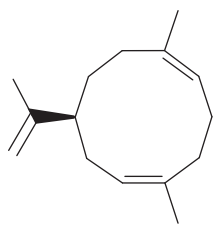
(a) 2,2,4-Trimethylhexane
(b) 2,2-Dimethylpropane
(c) 3-Ethyl-2,4,5-trimethyloctane
(d) 5-Butyl-2,2-dimethylnonane
(e) 4-Isopropyloctane
(f) 3,3-Dimethylpentane
(g) *trans*-1,3-Dimethylcyclopentane
(h) *cis*-1,2-Diethylcyclobutane

***3.26** Following is the structure of limonene, the chemical component of oranges that is partly responsible for their citrus scent. Draw the hydrogens present in limonene and classify those bonded to sp^3 hybridized carbons as 1°, 2°, or 3°. **(See Example 3.4)**



Limonene

***3.27** Following is the structure of Germacrene A, a hydrocarbon synthesized in plants and studied for its insecticidal properties. Classify each of the sp^3 hybridized carbons on Germacrene A as 1°, 2°, 3°, or 4°. **(See Example 3.4)**



Germacrene A

3.28 Explain why each of the following names is an incorrect IUPAC name and write the correct IUPAC name for the intended compound: **(See Examples 3.3, 3.5)**

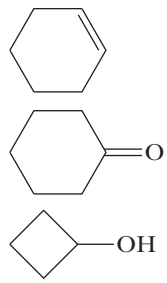
(a) 1,3-Dimethylbutane
(b) 4-Methylpentane
(c) 2,2-Diethylbutane
(d) 2-Ethyl-3-methylpentane
(e) 2-Propylpentane
(f) 2,2-Diethylheptane
(g) 2,2-Dimethylcyclopropane
(h) 1-Ethyl-5-methylcyclohexane

3.29 Draw a structural formula for each compound: **(See Example 3.6)**

(a) Ethanol
(b) Ethanal
(c) Ethanoic acid
(d) Butanone
(e) Butanal
(f) Butanoic acid
(g) Propanal
(h) Cyclopropanol
(i) Cyclopentanol
(j) Cyclopentene
(k) Cyclopentanone
(l) Heptanoic acid

3.30 Write the IUPAC name for each compound: **(See Example 3.6)**

(a) CH_3CCH_3 (O)
(b) $CH_3(CH_2)_3CH$ (O)
(c) $CH_3(CH_2)_8COH$ (O)



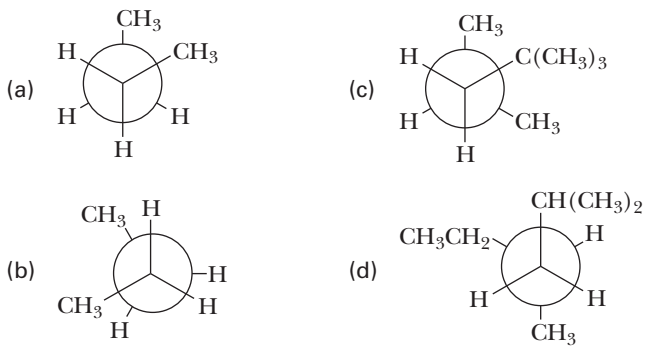
(d) (e) (f)

SECTION 3.6 Conformations of Alkanes and Cycloalkanes

3.31 How many *different* staggered conformations are there for 2-methylpropane? How many *different* eclipsed conformations are there?

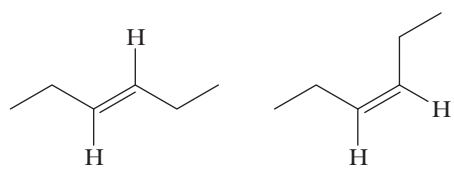
3.32 Looking along the bond between carbons 2 and 3 of butane, there are two different staggered conformations and two different eclipsed conformations. Draw Newman projections of each, and arrange them in order from the most stable conformation to the least stable conformation. **(See Example 3.7)**

3.33 Explain why each of the following Newman projections might not represent the most stable conformation of that molecule:

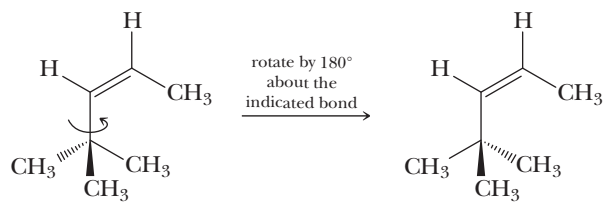


(a) (c) (b) (d)

3.34 Explain why the following are not different conformations of 3-hexene:

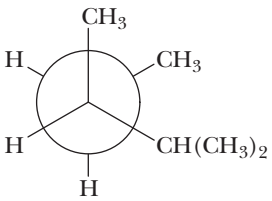
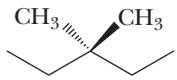


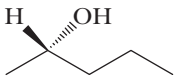
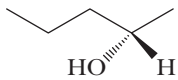
3.35 Which of the following two conformations is the more stable? (*Hint:* Use molecular models or draw Newman projections looking down the bond being rotated to compare structures):

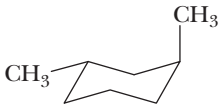
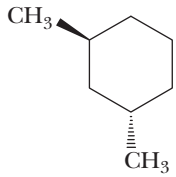


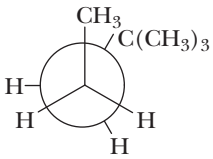
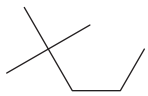
(a) (b)

3.36 Determine whether the following pairs of structures in each set represent the same molecule or constitutional isomers, and if they are the same molecule, determine whether they are in the same or different conformations:

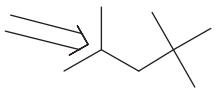
(a)  and 

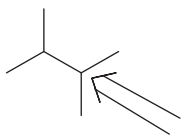
(b)  and 

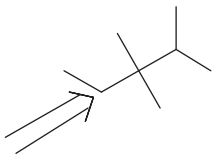
(c)  and 

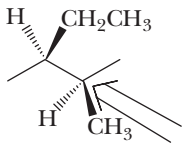
(d)  and 

3.37 Draw Newman projections for the most stable conformation of each of the following compounds looking down the indicated bond. **(See Example 3.7)**

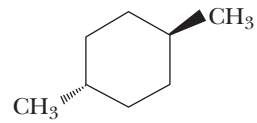
(a) 

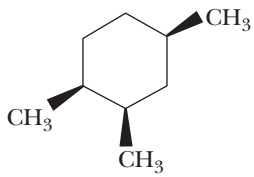
(c) 

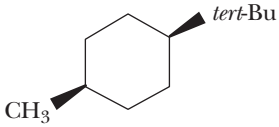
(b) 

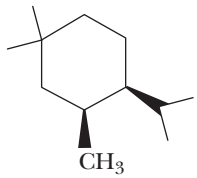
(d) 

3.38 Draw both chair forms of each of the following compounds and indicate the more stable conformation. **(See Examples 3.8, 3.9)**

(a) 

(c) 

(b) 

(d) 

SECTION 3.7 *Cis–Trans* Isomerism in Cycloalkanes

3.39 What structural feature of cycloalkanes makes *cis–trans* isomerism in them possible?

3.40 Is *cis–trans* isomerism possible in alkanes?

3.41 Name and draw structural formulas for the *cis* and *trans* isomers of 1,2-dimethylcyclopropane. **(See Examples 3.10, 3.11)**

3.42 Name and draw structural formulas for all cycloalkanes with the molecular formula C_5H_{10}. Be certain to include *cis–trans* isomers, as well as constitutional isomers. **(See Examples 3.10, 3.11)**

3.43 Using a planar pentagon representation for the cyclopentane ring, draw structural formulas for the *cis* and *trans* isomers of **(See Examples 3.10, 3.11)**

(a) 1,2-Dimethylcyclopentane

(b) 1,3-Dimethylcyclopentane

3.44 Draw the alternative chair conformations for the *cis* and *trans* isomers of 1,2-dimethylcyclohexane, 1,3-dimethylcyclohexane, and 1,4-dimethylcyclohexane. **(See Examples 3.10, 3.11)**

(a) Indicate by a label whether each methyl group is axial or equatorial.

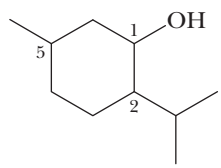
(b) For which isomer(s) are the alternative chair conformations of equal stability?

(c) For which isomer(s) is one chair conformation more stable than the other?

3.45 Use your answers from Problem 3.44 to complete the following table, showing correlations between *cis, trans* isomers and axial, equatorial positions for disubstituted derivatives of cyclohexane:

Position of Substitution	*cis*	*trans*
1,4-	a,e or e,a	e,e or a,a
1,3-	____ or ____	____ or ____
1,2-	____ or ____	____ or ____

***3.46** There are four *cis–trans* isomers of 2-isopropyl-5-methylcyclohexanol: **(See Examples 3.10, 3.11)**



2-Isopropyl-5-methylcyclohexanol

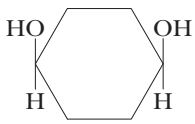
(a) Using a planar hexagon representation for the cyclohexane ring, draw structural formulas for these four isomers.

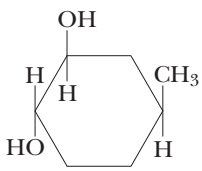
(b) Draw the more stable chair conformation for each of your answers in part (a).

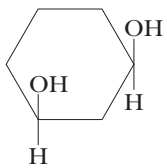
(c) Of the four *cis–trans* isomers, which is the most stable? If you answered this part correctly, you picked the isomer found in nature and given the name menthol.

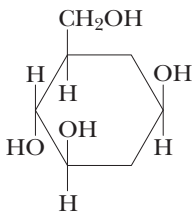
Peppermint plant (*Mentha piperita*), a source of menthol, is a perennial herb with aromatic qualities used in candies, gums, hot and cold beverages, and garnish for punch and fruit.

3.47 Draw alternative chair conformations for each substituted cyclohexane, and state which chair is the more stable: **(See Examples 3.8, 3.11)**

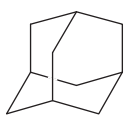
(a) 

(c) 

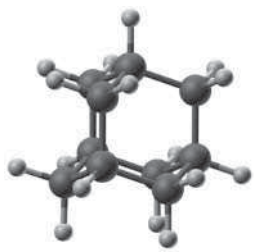
(b) 

(d) 

3.48 How many six-membered rings exist in adamantane? What kinds of conformations do the six-membered rings exhibit in adamantane? (*Hint:* Build a molecular model of the compound.)



Adamantane



SECTION 3.8 Physical Properties of Alkanes and Cycloalkanes

3.49 In Problem 3.21, you drew structural formulas for all constitutional isomers with the molecular formula C_7H_{16}. Predict which isomer has the lowest boiling point and which has the highest. **(See Example 3.12)**

3.50 What generalizations can you make about the densities of alkanes relative to that of water?

3.51 What unbranched alkane has about the same boiling point as water? (See Table 3.4.) Calculate the molecular weight of this alkane, and compare it with that of water. Explain why water, which is lower in mass than the alkane, boils at the same temperature.

3.52 As you can see from Table 3.4, each CH_2 group added to the carbon chain of an alkane increases the boiling point of the alkane. The increase is greater going from CH_4 to C_2H_6 and from C_2H_6 to C_3H_8 than it is from C_8H_{18} to C_9H_{20} or from C_9H_{20} to $C_{10}H_{22}$. What do you think is the reason for this trend?

3.53 Dodecane, $C_{12}H_{26}$, is an unbranched alkane. Predict the following:

(a) Will it dissolve in water?

(b) Will it dissolve in hexane?

(c) Will it burn when ignited?

(d) Is it a liquid, solid, or gas at room temperature and atmospheric pressure?

(e) Is it more or less dense than water?

***3.54** As stated in Section 3.8A, the wax found in apple skins is an unbranched alkane with the molecular formula $C_{27}H_{56}$. Explain how the presence of this alkane prevents the loss of moisture from within an apple.

SECTION 3.9 Reactions of Alkanes

3.55 Write balanced equations for the combustion of each hydrocarbon. Assume that each is converted completely to carbon dioxide and water.

(a) Hexane

(b) Cyclohexane

(c) 2-Methylpentane

***3.56** Following are heats of combustion of methane and propane:

Hydrocarbon	Component of	ΔH° [kJ/mol (kcal/mol)]
CH_4	natural gas	–886 (–212)
$CH_3CH_2CH_3$	LPG	–2220 (–530)

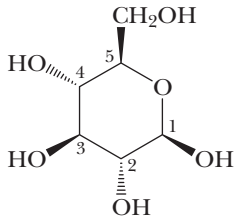
On a gram-for-gram basis, which of these hydrocarbons is the better source of heat energy?

***3.57** When ethanol is added to gasoline to produce gasohol, the ethanol promotes more complete combustion of the gasoline and is an octane booster (Section 3.10B). Compare the heats of combustion of 2,2,4-trimethylpentane 5460 kJ/mol (1304 kcal/mol) and ethanol 1369 kJ/mol (327 kcal/mol). Which has the higher heat of combustion in kJ/mol? in kJ/g?

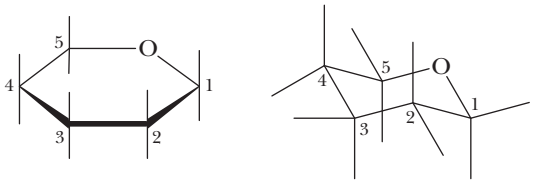
LOOKING AHEAD

3.58 Explain why 1,2-dimethylcyclohexane can exist as *cis–trans* isomers, while 1,2-dimethylcyclododecane cannot.

***3.59** Following is a representation of the glucose molecule (we discuss the structure and chemistry of glucose in Chapter 17):



Glucose

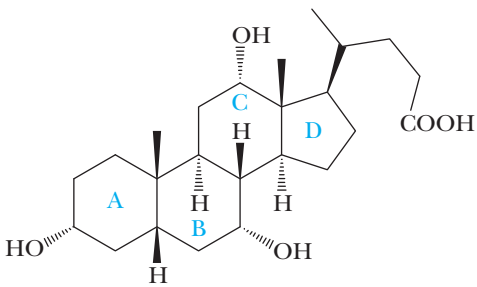


(a) (b)

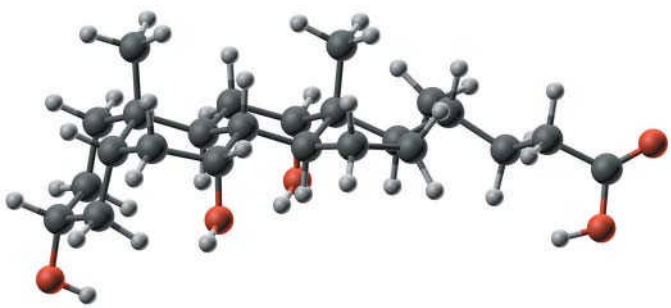
(a) Convert this representation to a planar hexagon representation.

(b) Convert this representation to a chair conformation. Which substituent groups in the chair conformation are equatorial? Which are axial?

***3.60** Following is the structural formula of cholic acid (Section 19.4A), a component of human bile whose function is to aid in the absorption and digestion of dietary fats:



Cholic acid



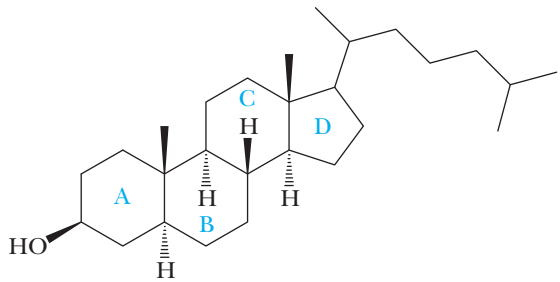
(a) What are the conformations of rings A, B, C, and D?

(b) There are hydroxyl groups on rings A, B, and C. Tell whether each is axial or equatorial.

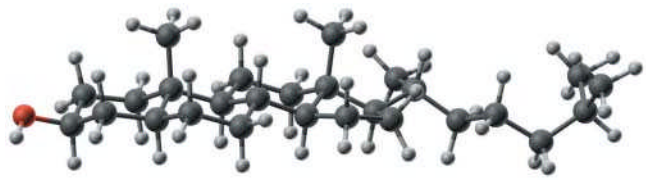
(c) Is the methyl group at the junction of rings A and B axial or equatorial to ring A? Is it axial or equatorial to ring B?

(d) Is the methyl group at the junction of rings C and D axial or equatorial to ring C?

***3.61** Following is the structural formula and ball-and-stick model of cholestanol:



Cholestanol



The only difference between this compound and cholesterol (Section 19.4A) is that cholesterol has a carbon–carbon double bond in ring B.

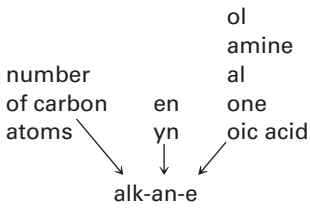
(a) Describe the conformation of rings A, B, C, and D in cholestanol.

(b) Is the hydroxyl group on ring A axial or equatorial?

(c) Consider the methyl group at the junction of rings A and B. Is it axial or equatorial to ring A? Is it axial or equatorial to ring B?

(d) Is the methyl group at the junction of rings C and D axial or equatorial to ring C?

3.62 As we have seen in Section 3.4, the IUPAC system divides the name of a compound into a prefix (showing the number of carbon atoms), an infix (showing the presence of carbon–carbon single, double, or triple bonds), and a suffix (showing the presence of an alcohol, amine, aldehyde, ketone, or carboxylic acid). Assume for the purposes of this problem that, to be alcohol (-ol) or amine (-amine), the hydroxyl or amino group must be bonded to a tetrahedral (sp^3 hybridized) carbon atom.



Given this information, write the structural formula of a compound with an unbranched chain of four carbon atoms that is an:

(a) Alkane
(b) Alkene
(c) Alkyne
(d) Alkanol
(e) Alkenol
(f) Alkynol
(g) Alkanamine
(h) Alkenamine
(i) Alkynamine
(j) Alkanal
(k) Alkenal
(l) Alkynal
(m) Alkanone
(n) Alkenone
(o) Alkynone
(p) Alkanoic acid
(q) Alkenoic acid
(r) Alkynoic acid

(*Note:* There is only one structural formula possible for some parts of this problem. For other parts, two or more structural formulas are possible. Where two or more are possible, we will deal with how the IUPAC system distinguishes among them when we come to the chapters on those particular functional groups.)

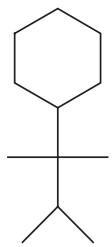
GROUP LEARNING ACTIVITIES

***3.63** Come up with reasons for the following phenomena. You may need to refer to concepts learned from previous chapters or from general chemistry.

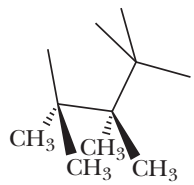
(a) Gasoline is cool to the touch when spilled on bare skin.
(b) Water is more dense than methane.
(c) Butane is a more appropriate fuel for a disposable lighter than either propane or pentane.

3.64 See who can name the following stick figure molecules the fastest:

(a)



(b)



PUTTING IT TOGETHER

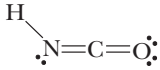
The following problems bring together concepts and material from Chapters 1–3.

Choose the best answer for each of the following questions.

1. Which of the following molecules has a net charge of +1?

(a) CH_2CHCH_3
(b) CH_3CHCH_3
(c) $CHCCH_3$
(d) $(CH_3)_3CH$
(e) CH_2CH_2

2. Which of the following statements is true concerning the following compound?

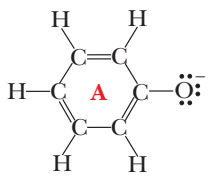


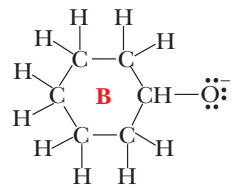
(a) The central carbon is sp^2 hybridized, and the molecule is planar in geometry.
(b) The central carbon is sp^2 hybridized, and the molecule is nonplanar in geometry.
(c) The central carbon is *sp* hybridized, and the molecule is planar in geometry.
(d) The central carbon is *sp* hybridized, and the molecule is nonplanar in geometry.
(e) None of these statements is true.

3. Which of the following statements is false concerning *p* orbitals?

(a) They consist of two equivalent lobes.
(b) They are absent from the first shell of atomic orbitals.
(c) They can form π bonds.
(d) They only participate in bonding on carbon atoms.
(e) They can hold a maximum of two electrons.

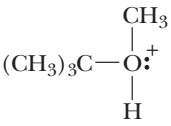
4. Which base (A or B) is stronger and why?

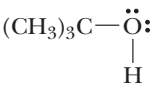


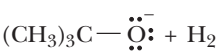


(a) **A** is stronger because it has fewer protons for the acid to compete with in acid–base reactions.
(b) **A** is stronger because inductive effects increase the negative character of its oxygen.
(c) **B** is stronger because inductive effects increase the negative character of its oxygen.
(d) **B** is stronger because resonance effects can delocalize its negative charge throughout the molecule.
(e) **B** is stronger because it has no resonance or inductive effects that can delocalize its negative charge throughout the molecule.

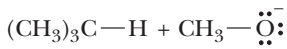
5. Which of the following is the initial product of the reaction between $(CH_3)_3C^+$ and CH_3OH?

(a) 

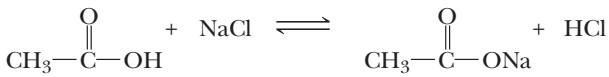
(b) 

(c) 

(d) 

(e) 

6. Select the statement that is false concerning the following acid–base reaction.



(a) The equilibrium lies on the product side of the reaction.

(b) The carboxylic acid does not possess a positive charge.

(c) The chloride ion acts as a Lewis base.

(d) The chloride ion acts as a Brønsted–Lowry base.

(e) The carboxylic acid is a weaker acid than HCl.

7. Which of the following statements is false?

(a) Nonbonded interaction (steric) strain contributes to the energy of butane in the eclipsed conformation.

(b) All staggered conformations possess zero strain.

(c) A Newman projection is the picture of a molecule viewed down at least one of its bonds.

(d) Bonds represented by Newman projections do not freely rotate because they must overcome an energy barrier to rotation.

(e) Ring strain contributes to the instability of cyclopropane.

8. Which of the following statements is true concerning the isomers *cis*-1,2-dimethylcyclohexane and *cis*-1,3-dimethylcyclohexane?

(a) They are not constitutional isomers.

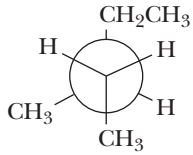
(b) They are conformers.

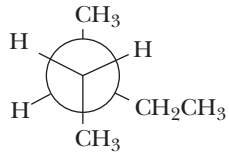
(c) The favored conformer of the 1,3-isomer is more stable than that of the 1,2-isomer.

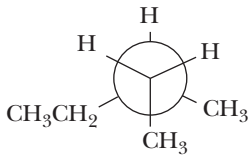
(d) The favored conformer of the 1,3-isomer and that of the 1,2-isomer are equal in energy.

(e) The relative stability of the two molecules cannot be predicted.

9. Select the correct order of stability (least stable → most stable) for the following conformations.

(a) 

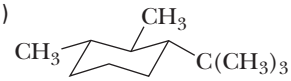
(b) 

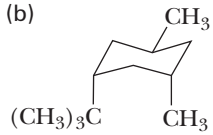
(c) 

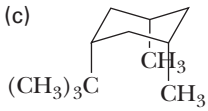
(a) a, b, c (c) b, a, c (e) c, b, a

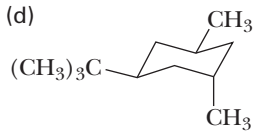
(b) a, c, b (d) c, a, b

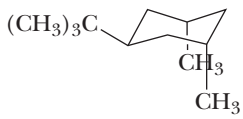
10. Select the most stable conformation of those shown for 1-*tert*-butyl-3,5-dimethylcyclohexane.

(a) 

(b) 

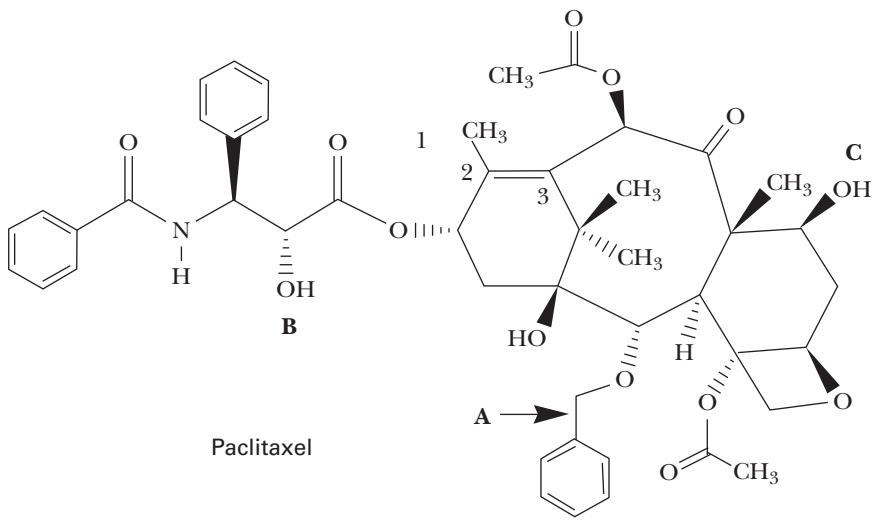
(c) 

(d) 

(e) 

***11.** Answer the questions that follow regarding the structure of paclitaxel (trade name Taxol®), a compound first isolated from the Pacific Yew tree, which is now used to treat ovarian, breast, and non–small cell lung cancer.

(a) Identify all the hydroxy groups and classify them as 1°, 2°, or 3°.



Paclitaxel

(b) Identify all the carbonyl groups. Are any of them part of an aldehyde, a ketone, or a carboxylic acid?

(c) What atomic or hybridized orbitals participate in the bond labeled **A**?

(d) Are there any quaternary carbons in paclitaxel?

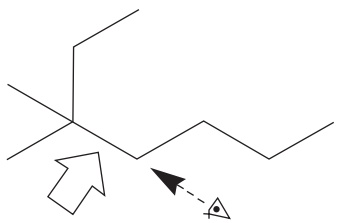
(e) Explain why hydroxyl group **B** is more acidic than hydroxyl group **C**.

(f) What is the angle of the bond containing atoms 1–2–3?

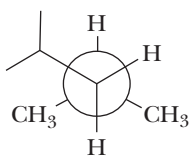
(g) Locate any amide functional groups. How many are there?

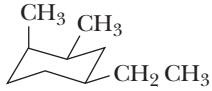
(h) Locate any ester functional groups. How many are there?

12. Draw Newman projections of the three most stable conformations of the following compound viewed down the indicated bond and in the indicated direction. Indicate the most favorable conformation. You should be able to briefly describe or illustrate why your choice is the most favorable conformation.



13. Provide IUPAC names for the following compounds.

(a) 

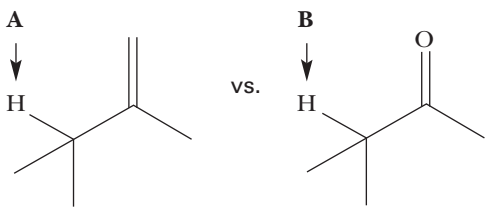
(b) 

(c) $CH_3CH_2CH(CH_3)CH(CH_2CH_3)CH_2CH(CH_3)_2$

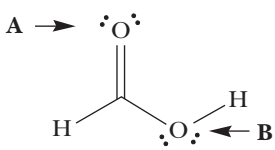
14. For each pair of molecules, select the one that best fits the accompanying description. Provide a concise but thorough rationale for each of your decisions using words and/or pictures.

(a) The higher boiling point?

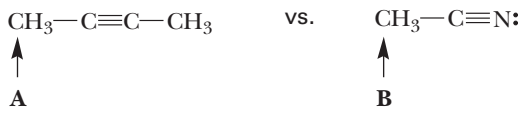
(b) The more acidic hydrogen?



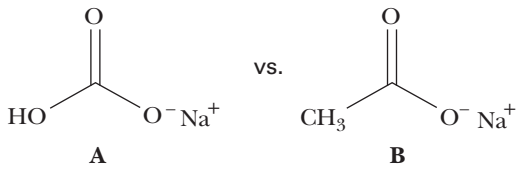
(c) The more basic atom?



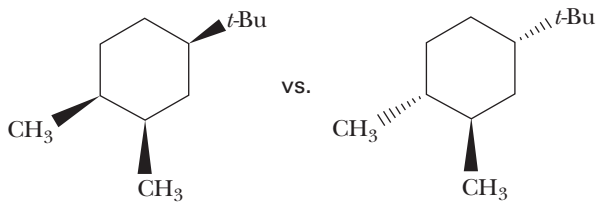
(d) The more acidic set of protons?



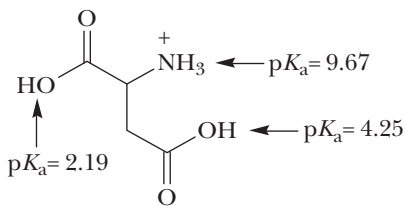
(e) The stronger base?



(f) Possesses the least nonbonding interaction (steric) strain?

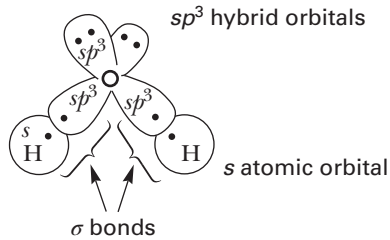


***15.** Glutamic acid is one of the common amino acids found in nature. Draw the predominant structure of glutamic acid when placed in a solution of p*H* = 3.2 and indicate its overall charge.



16. Use atomic and hybridized orbitals to illustrate (see example using H_2O) the location of bonding and non-bonding electrons in ethenimine. Do all of the atoms in ethenimine lie in the same plane?

Example orbital illustration for H_2O



$HN{=}C{=}CH_2$
Ethenimine

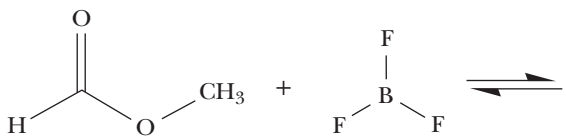
17. The following values have been determined for the amount of energy it takes to place a substituent in the axial position. As shown in the table, going from H to CH_3 causes a drastic increase in free energy (7.28 kJ/mol). However, increasing the size of the R group results in only a minor change in ΔG even when the R group is isopropyl (this only increases ΔG by 1.72 kJ/mol over methyl). *Using perspective* (*dash-wedge*) *drawings*, illustrate and explain why the increase in

ΔG is only gradual up to isopropyl but increases drastically when the R group is *t*-butyl.

R	ΔG kJ/mol (kcal/mol)
H	0
CH_3	7.28 (1.74)
CH_2CH_3	7.32 (1.75)
$CH(CH_3)_2$	9.00 (2.15)
$C(CH_3)_3$	20.92 (5.00)

18. (a) Draw the two possible products that can form from the Lewis acid–base reaction between methyl formate and BF_3. Indicate the major product and use curved arrow notation to illustrate its formation. Show all charges and nonbonded electrons *in your products*.

(b) Use pictures and words to explain why the product you indicated is favored over the other product.



Methyl formate

19. Use resonance theory to predict whether $[CNO]^-$ or $[NCO]^-$ is the more stable ion. Use pictures *and* words to explain your decision.

20. Provide structures as indicated:

(a) All compounds with the molecular formula C_5H_{10} that exhibit *cis–trans* isomerism.

(b) Lewis structures and any resonance structures for the ion with formula CH_2NO_2. Show all formal charges and lone pairs of electrons.

(c) All compounds that upon combustion with 6 mol of O_2 would yield 4 mol of CO_2 and 4 mol of H_2O.

***21.** Teixobactin is a new class of anitbiotic that disrupts the ability of gram positive bacteria to form its cell wall. It is currently being developed as an antibiotic for *Staphylococcus aureus* and *Mycobacterium tuberculosis* because these bacteria do not develop resistance to teixobactin as they do to other antibiotics.

(a) Locate all of the amide functional groups in teixobactin.

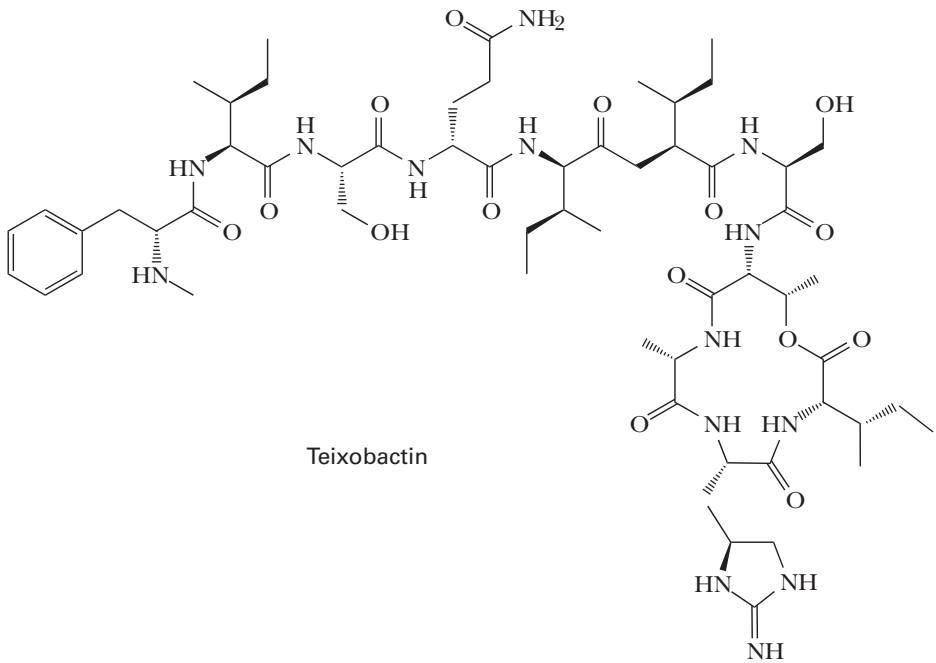
(b) Locate all of the amine functional groups in teixobactin and classify them as 1°, 2°, or 3°.

(c) Locate all of the ester functional groups in teixobactin.

(d) Locate all of the alcohol functional groups in teixobactin and classify them as 1°, 2°, or 3°.

(e) Label all of the 1°, 2°, or 3° carbons in teixobactin.

(f) Draw lone pairs of nonbonded electrons for all atoms where they have been left out.



Teixobactin

Alkenes and Alkynes

Charles D. Winters

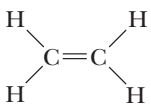
Carotene and carotene-like molecules are alkene-containing compounds in nature that assist in the harvest of sunlight. The red color of tomatoes comes from lycopene, a molecule closely related to carotene. See Problems 4.37 and 4.38. Inset: A model of β-carotene.

4

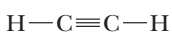
IN THIS CHAPTER, we begin our study of unsaturated hydrocarbons, compounds of carbon and hydrogen that contain at least one pi bond. Look at the two compounds shown below. Ethene is an **alkene**, a hydrocarbon containing one or more carbon–carbon double bonds, and ethyne is an **alkyne**, a hydrocarbon containing one or more carbon—carbon triple bonds.

Alkene An unsaturated hydrocarbon that contains a carbon–carbon double bond.

Alkyne An unsaturated hydrocarbon that contains a carbon–carbon triple bond.



Ethene
(an alkene)



Ethyne
(an alkyne)

Arenes are the third class of unsaturated hydrocarbons and are represented by the compound benzene. How is benzene structurally similar to either ethene or ethyne? How is it different? One unobvious but very important difference is that the chemistry of benzene and its derivatives is quite different from that of alkenes and alkynes. We don't study the chemistry of arenes until Chapter 9, but we will encounter many compounds containing benzene rings. What you need to remember at this point is that a benzene ring is not chemically reactive under any of the conditions we describe in Chapters 4–8. In other words, their pi bonds will remain unchanged (at least until we get to Chapter 9).

Arenes A compound containing one or more benzene rings.

Chemical Connections 4A

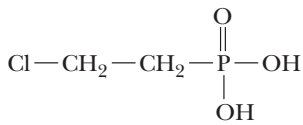
ETHYLENE, A PLANT GROWTH REGULATOR

Ethylene occurs only in trace amounts in nature. Still, scientists have discovered that this small molecule is a natural ripening agent for fruits. Thanks to this knowledge, fruit growers can pick fruit while it is green and less susceptible to bruising. Then, when they are ready to pack the fruit for shipment, the growers can treat it with ethylene gas to induce ripening. Alternatively, the fruit can be treated with ethephon (Ethrel), which slowly releases ethylene and initiates ripening.

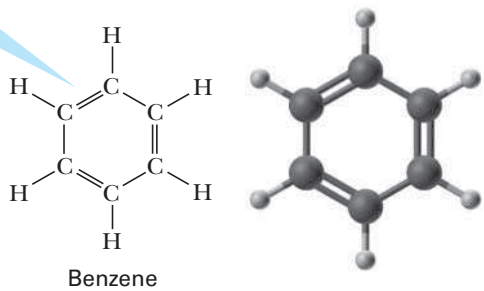
The next time you see ripe bananas in the market, you might wonder when they were picked and whether their ripening was artificially induced.

Question

Explain the basis for the saying "A rotten apple can spoil the barrel."

Ethephon 

although benzene and other arenes contain C–C double bonds, we must remember that their double bonds are not reactive in the ways we will describe in Chapters 4–8 (i.e., we will leave them unreacted in reactions that we cover in these chapters)



Benzene
(an arene)

Compounds containing carbon–carbon double bonds are especially widespread in nature. Ethylene, for example, is produced by all higher order plants. Furthermore, several low-molecular-weight alkenes, including ethylene and propene, have enormous commercial importance in our modern, industrialized society. The organic chemical industry produces more pounds of ethylene worldwide than any other chemical. Annual production in the United States alone exceeds 20 billion kg (45 billion pounds).

What is unusual about ethylene is that it occurs only in trace amounts in nature. The enormous amounts of it required to meet the needs of the chemical industry are derived the world over by thermal cracking of hydrocarbons. In the United States and other areas of the world with vast reserves of natural gas, the major process for the production of ethylene is thermal cracking of the small quantities of ethane extracted from natural gas. In **thermal cracking**, a saturated hydrocarbon is converted to an unsaturated hydrocarbon plus H_2. Heating ethane in a furnace to 800–900 °C for a fraction of a second cracks it to ethylene and hydrogen.

$$\underset{\text{Ethane}}{CH_3CH_3} \xrightarrow[\text{(thermal cracking)}]{800\text{–}900\ ^\circ C} \underset{\text{Ethylene}}{CH_2{=}CH_2} + H_2$$

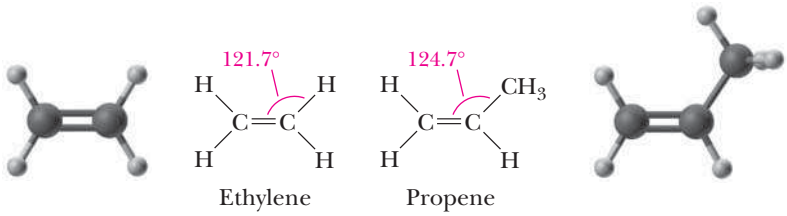
Europe, Japan, and other areas of the world with limited supplies of natural gas depend almost entirely on thermal cracking of petroleum for their ethylene.

The crucial point to recognize is that ethylene and all of the commercial and industrial products made from it are derived from either natural gas or petroleum—both nonrenewable natural resources!

4.1 What Are the Structures and Shapes of Alkenes and Alkynes?

A. Shapes of Alkenes

Using valence-shell electron-pair repulsion (VSEPR; Section 1.3), we predict a value of 120° for the bond angles about each carbon in a double bond. The observed H—C—C bond angle in ethylene is 121.7°, a value close to that predicted by VSEPR. In other alkenes, deviations from the predicted angle of 120° may be somewhat larger as a result of strain between groups bonded to one or both carbons of the double bond. The C—C—C bond angle in propene, for example, is 124.7°.



B. Orbital Overlap Model of a Carbon–Carbon Double Bond

In Section 1.6D, we described the formation of a carbon–carbon double bond in terms of the overlap of atomic orbitals. A carbon–carbon double bond consists of one sigma bond and one pi bond. It takes approximately 264 kJ/mol (63 kcal/mol) to break the pi bond in ethylene—that is, to rotate one carbon by 90° with respect to the other so that no overlap occurs between 2*p* orbitals on adjacent carbons (Figure 4.1). This energy is considerably greater than the thermal energy available at room temperature, and, as a consequence, rotation about a carbon–carbon double bond is severely restricted. You might compare rotation about a carbon–carbon double bond to that about a carbon–carbon single bond, such as the bond in ethane (Section 3.6A) where the energy barrier is only 13 kJ/mol.

***Cis–trans* isomerism** Isomers that have the same order of attachment (connectivity) of their atoms, but a different arrangement of their atoms in space due to the presence of either a ring (Chapter 3) or a carbon–carbon double bond (Chapter 4).

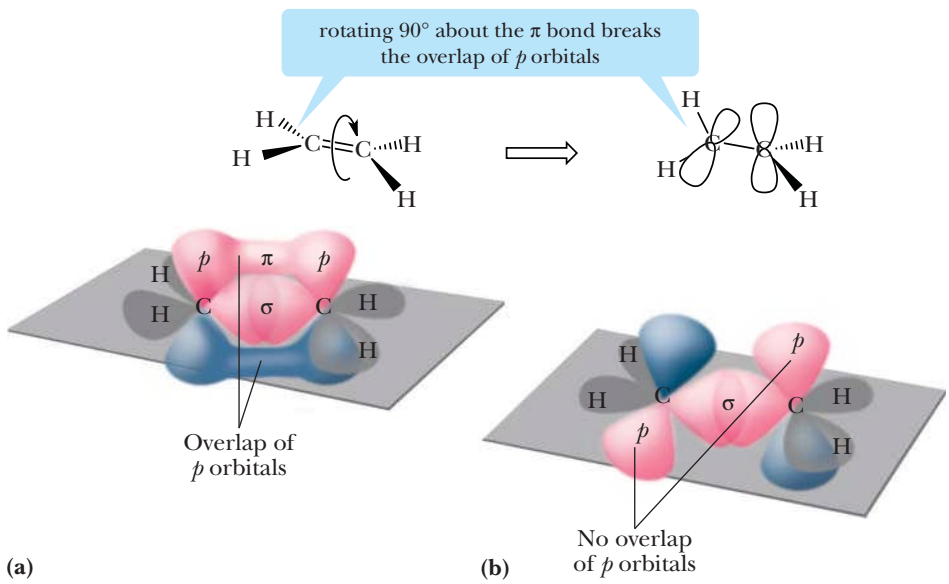


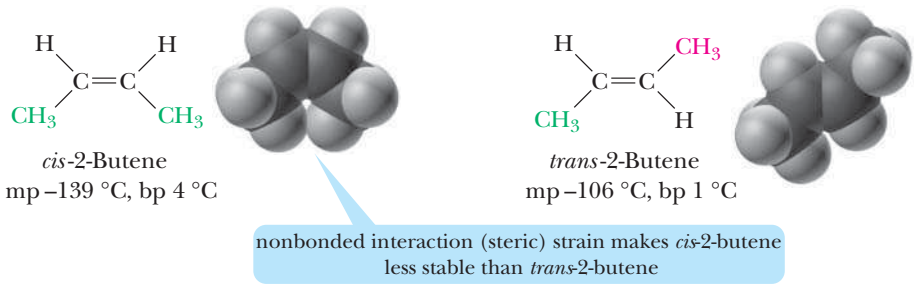
FIGURE 4.1 Restricted rotation about the carbon–carbon double bond in ethylene. (a) Orbital overlap model showing the pi bond. (b) The pi bond is broken by rotating the plane of one H—C—H group by 90° with respect to the plane of the other H—C—H group.

C. *Cis–Trans* Isomerism in Alkenes

Because of restricted rotation about a carbon–carbon double bond, an alkene in which each carbon of the double bond has two different groups bonded to it shows ***cis–trans isomerism***.

Charles D. Winters

The combustion of acetylene yields energy that produces the very hot temperatures of an oxyacetylene torch.



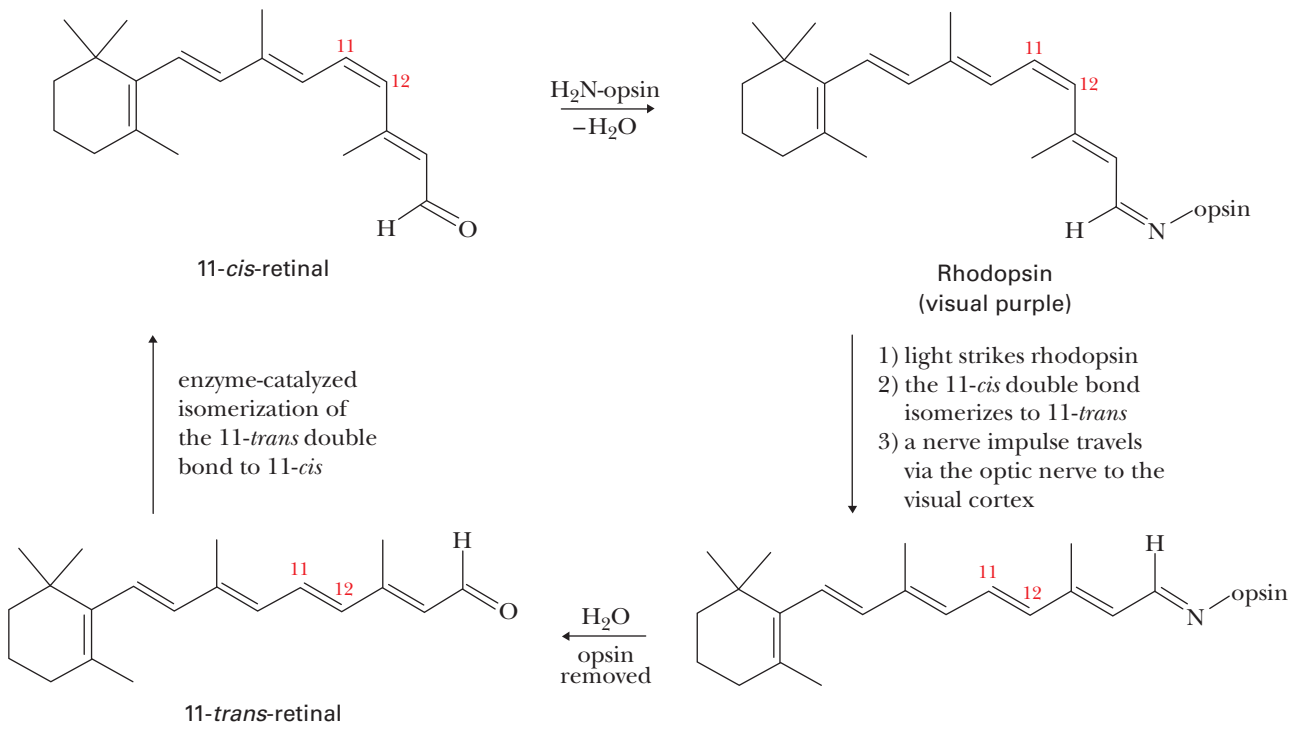
Consider, for example, 2-butene: In *cis*-2-butene, the two methyl groups are on the same side of the double bond; in *trans*-2-butene, the two methyl groups are on opposite sides of the double bond. These two compounds cannot be converted into one another at room temperature because of the restricted rotation about the double bond; they are different compounds, with different physical and chemical properties.

Cis alkenes are less stable than their *trans* isomers because of nonbonded interaction strain between alkyl substituents on the same side of the double bond in the *cis* isomer, as can be seen in space-filling models of the *cis* and *trans* isomers of 2-butene. This is the same type of steric strain that results in the preference for equatorial methylcyclohexane over axial methylcyclohexane (Section 3.6B).

Chemical Connections 4B

CIS–TRANS ISOMERISM IN VISION

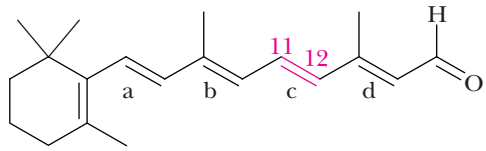
The retina—the light-detecting layer in the back of our eyes—contains reddish compounds called *visual pigments*. Their name, *rhodopsin*, is derived from the Greek word meaning "rose colored." Each rhodopsin molecule is a combination of one molecule of a protein called opsin and one molecule of 11-*cis*-retinal, a derivative of vitamin A in which the CH_2OH group of the vitamin is converted to an aldehyde group, —CHO, and the double bond between carbons 11 and 12 of the side chain is in the less stable *cis* configuration. When rhodopsin absorbs light energy, the less stable 11-*cis* double bond is converted to the more stable 11-*trans* double bond. This isomerization changes the shape of the rhodopsin molecule, which in turn causes the neurons of the optic nerve to fire and produce a visual image.



The retina of vertebrates has two kinds of cells that contain rhodopsin: rods and cones. Cones function in bright light and are used for color vision; they are concentrated in the central portion of the retina, called the *macula*, and are responsible for the greatest visual acuity. The remaining area of the retina consists mostly of rods, which are used for peripheral and night vision. 11-*cis*-Retinal is present in both cones and rods. Rods have one kind of opsin, whereas cones have three kinds—one for blue, one for green, and one for red color vision.

Question

The four *trans* double bonds in the side chain of retinal are labeled a–d. Double bond c (between carbons 11 and 12) is isomerized to its *cis* isomer by an enzyme in the body. Which of the other three double bonds in the side chain of retinal would yield the least stable isomer of *cis* retinal if it were to be isomerized? (*Hint:* Think steric strain.)



11-*trans*-retinal

D. Structure of Alkynes

The functional group of an alkyne is a **carbon–carbon triple bond**. The simplest alkyne is ethyne, C_2H_2. Ethyne is a linear molecule; all of its bond angles are 180° (Figure 1.10).

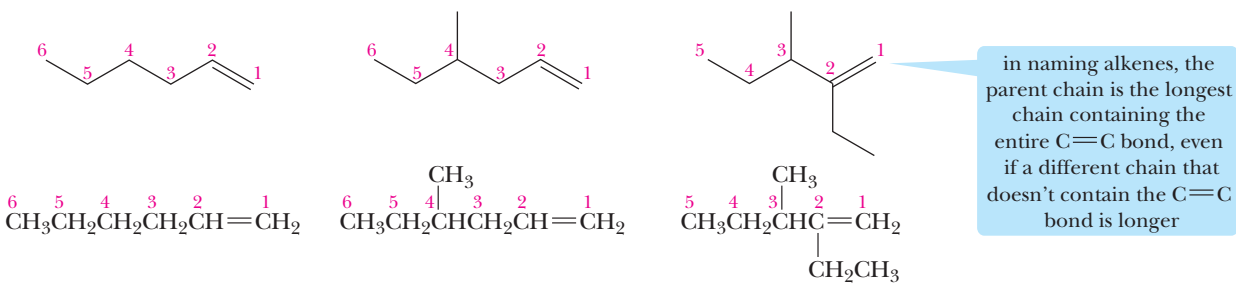
According to the orbital overlap model (Section 1.6F), a triple bond is described in terms of the overlap of *sp* hybrid orbitals of adjacent carbons to form a sigma bond, the overlap of parallel $2p_y$ orbitals to form one pi bond, and the overlap of parallel $2p_z$ orbitals to form the second pi bond. In ethyne, each carbon forms a bond to a hydrogen by the overlap of an *sp* hybrid orbital of carbon with a 1*s* atomic orbital of hydrogen.

4.2 How Do We Name Alkenes and Alkynes?

Alkenes are named using the IUPAC system, but, as we shall see, some are still referred to by their common names.

A. IUPAC Names

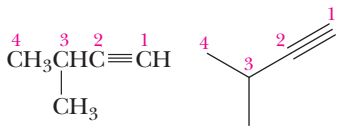
We form IUPAC names of alkenes by changing the **-an-** infix of the parent alkane to **-en-** (Section 3.5). Hence, $CH_2{=}CH_2$ is named ethene, and $CH_3CH{=}CH_2$ is named propene. In higher alkenes, where isomers exist that differ in the location of the double bond, we use a numbering system. We number the longest carbon chain that contains the double bond in the direction that gives the carbon atoms of the double bond the lower set of numbers. We then use the number of the first carbon of the double bond to show its location. We name branched or substituted alkenes in a manner similar to the way we name alkanes (Section 3.3). We number the carbon atoms, locate the double bond, locate and name substituent groups, and name the main (parent) chain.



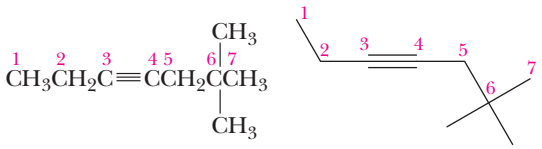
1-Hexene 4-Methyl-1-hexene 2-Ethyl-3-methyl-1-pentene

Note that there is a six-carbon chain in 2-ethyl-3-methyl-1-pentene. However, because the longest chain that contains the carbon–carbon double bond has only five carbons, the parent hydrocarbon is pentane, and we name the molecule as a disubstituted 1-pentene.

We form IUPAC names of alkynes by changing the **-an-** infix of the parent alkane to **-yn-** (Section 3.5). Thus, HC≡CH is named ethyne, and $CH_3C{\equiv}CH$ is named propyne. The IUPAC system retains the name *acetylene*; therefore, there are two acceptable names for HC≡CH: *ethyne* and *acetylene*. Of these two names, *acetylene* is used much more frequently. For larger molecules, we number the longest carbon chain that contains the triple bond from the end that gives the triply bonded carbons the lower set of numbers. We indicate the location of the triple bond by the number of the first carbon of the triple bond.



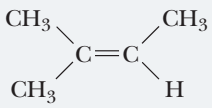
3-Methyl-1-butyne



6,6-Dimethyl-3-heptyne

EXAMPLE 4.1

Write the IUPAC name of each unsaturated hydrocarbon:

(a) $CH_2{=}CH(CH_2)_5CH_3$ **(b)**  **(c)** $CH_3(CH_2)_2C{\equiv}CCH_3$

STRATEGY

First look for the longest carbon chain that contains the multiple bond. This chain determines the root name. Number the carbon chain to give the placement of the multiple bond the lowest possible set of numbers. Then identify substituents and give each a name and a number. Locate the position of the multiple bond by the number of its first carbon.

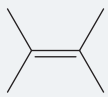
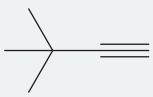
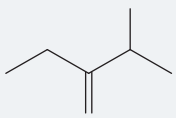
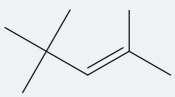
SOLUTION

(a) 1-Octene **(b)** 2-Methyl-2-butene **(c)** 2-Hexyne

See problems 4.15–4.20

PROBLEM 4.1

Write the IUPAC name of each unsaturated hydrocarbon:

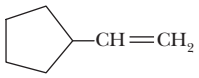
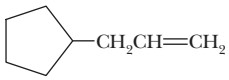
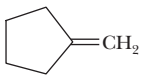
(a)  **(b)**  **(c)**  **(d)**  **(e)** 

B. Common Names

Despite the precision and universal acceptance of IUPAC nomenclature, some alkenes, particularly those with low molecular weight, are known almost exclusively by their common names, as illustrated by the common names of these alkenes:

	$CH_2{=}CH_2$	$CH_3CH{=}CH_2$	$CH_3C(CH_3){=}CH_2$
IUPAC name:	Ethene	Propene	2-Methylpropene
Common name:	Ethylene	Propylene	Isobutylene

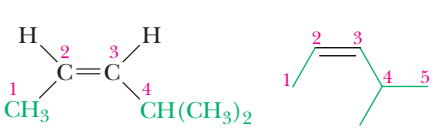
Furthermore, the common names **methylene** (a CH_2 group), **vinyl**, and **allyl** are often used to show the presence of the following alkenyl groups.

Alkenyl Group	Common Name	Example	Common Name
$CH_2{=}CH{-}$	Vinyl		Vinylcyclopentane
$CH_2{=}CHCH_2{-}$	Allyl		Allylcyclopentane
$CH_2{=}$	Methylene		Methylenecyclopentane

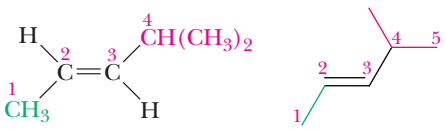
C. Systems for Designating Configuration in Alkenes

The *Cis–Trans* System

The most common method for specifying the configuration of a disubstituted alkene uses the prefixes *cis* and *trans*. In this system, the orientation of the atoms of the parent chain determines whether the alkene is *cis* or *trans*. Following are structural formulas for the *cis* and *trans* isomers of 4-methyl-2-pentene:



cis-4-Methyl-2-pentene

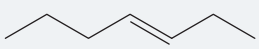
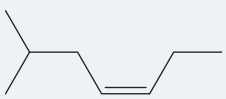


trans-4-Methyl-2-pentene

In the *cis* example, carbon atoms of the main chain (carbons 1 and 4) are on the same side of the double bond. In the *trans* example, the same carbon atoms of the main chain are on opposite sides of the double bond.

EXAMPLE 4.2

Name each alkene, and, using the *cis–trans* system, show the configuration about each double bond:

(a)  **(b)** 

STRATEGY

Locate the longest carbon chain that contains the multiple bond and number it from the end that gives the lower set of numbers to the carbon atoms of the multiple bond. Indicate the location of the multiple bond by the number of its first carbon atom. Configuration of a carbon–carbon double bond (*cis* or *trans*) in a common name is determined by the orientation of the carbon atoms of the parent chain relative to each other. If you are having difficulty discerning the orientation of the carbon atoms, draw in the hydrogen atoms on the C═C bond and determine their orientation relative to each other.

SOLUTION

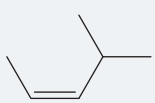
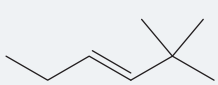
(a) The chain contains seven carbon atoms and is numbered from the end that gives the lower number to the first carbon of the double bond. The carbon atoms of the parent chain are on opposite sides of the double bond. The compound's name is *trans*-3-heptene.

(b) The longest chain contains seven carbon atoms and is numbered from the right, so that the first carbon of the double bond is carbon 3 of the chain. The carbon atoms of the parent chain are on the same side of the double bond. The compound's name is *cis*-6-methyl-3-heptene.

See problems 4.21, 4.22

PROBLEM 4.2

Name each alkene, and, using the *cis–trans* system, specify its configuration:

(a)  **(b)** 

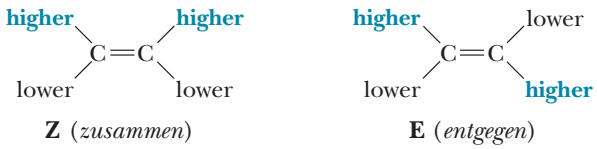
The E,Z System

E,Z system A system used to specify the configuration of groups about a carbon–carbon double bond.

Z From the German *zusammen*, meaning together; specifies that groups of higher priority on the carbons of a double bond are on the same side.

E From the German *entgegen*, meaning opposite; specifies that groups of higher priority on the carbons of a double bond are on opposite sides.

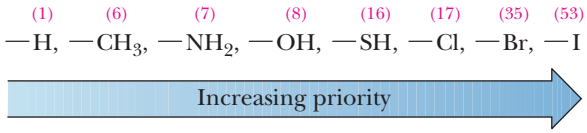
The **E,Z system** must be used for tri- and tetrasubstituted alkenes. This system uses a set of rules to assign priorities to the substituents on each carbon of a double bond. If the groups of higher priority are on the same side of the double bond, the configuration of the alkene is **Z** (German: *zusammen*, together). If the groups of higher priority are on opposite sides of the double bond, the configuration is **E** (German: *entgegen*, opposite).



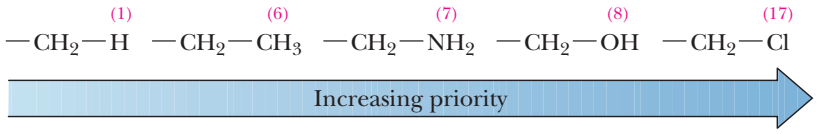
The first step in assigning an E or a Z configuration to a double bond is to label the two groups bonded to each carbon in order of priority.

Priority Rules

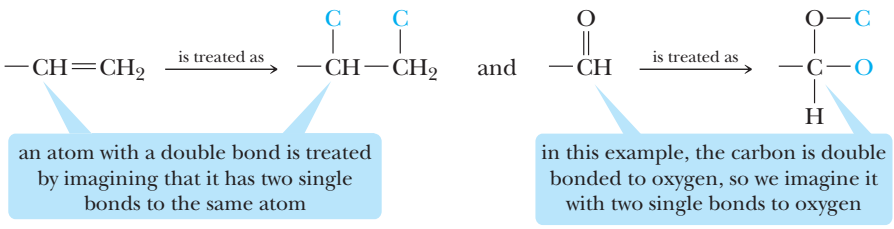
1. Priority is based on atomic number: The higher the atomic number, the higher is the priority. Following are several substituents arranged in order of increasing priority (the atomic number of the atom determining priority is shown in parentheses):



2. If priority cannot be assigned on the basis of the atoms that are bonded directly to the double bond, look at the next set of atoms, and continue until a priority can be assigned. Priority is assigned at the first point of difference. Following is a series of groups, arranged in order of increasing priority (again, numbers in parentheses give the atomic number of the atom on which the assignment of priority is based):



3. In order to compare carbons that are not sp^3 hybridized, the carbons must be manipulated in a way that allows us to maximize the number of groups bonded to them. Thus, we treat atoms participating in a double or triple bond as if they are bonded to an equivalent number of similar atoms by single bonds; that is, atoms of a double bond are replicated. Accordingly,



EXAMPLE 4.3

Assign priorities to the groups in each set:

(a) —COH and —CH (O)

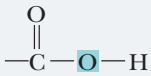
(b) —CH_2NH_2 and —COH (O)

STRATEGY

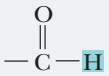
Priority is based on atomic number; the higher the atomic number, the higher the priority. If priority cannot be determined on the basis of the atoms bonded directly to the carbon–carbon double bond, continue to the next set of atoms and continue in this manner until a priority can be assigned.

SOLUTION

(a) The first point of difference is the O of the —OH in the carboxyl group, compared with the —H in the aldehyde group. The carboxyl group is higher in priority:



Carboxyl group (higher priority)



Aldehyde group (lower priority)

(b) Oxygen has a higher priority (higher atomic number) than nitrogen. Therefore, the carboxyl group has a higher priority than the primary amino group:

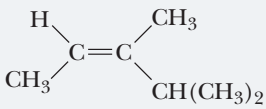
lower priority

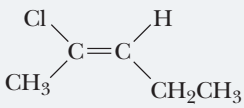
higher priority

See problems 4.23, 4.27, 4.28, 4.32

EXAMPLE 4.4

Name each alkene and specify its configuration by the E,Z system:

(a) 

(b) 

STRATEGY

Assign a priority to each atom or group of atoms on the carbon–carbon double bond. If the groups of higher priority are on the same side of the double bond, the alkene has the Z configuration; if they are on opposite sides, the alkene has the E configuration.

SOLUTION

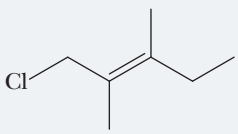
(a) The group of higher priority on carbon 2 is methyl; that of higher priority on carbon 3 is isopropyl. Because the groups of higher priority are on the same side of the carbon–carbon double bond, the alkene has the Z configuration. Its name is (*Z*)-3,4-dimethyl-2-pentene.

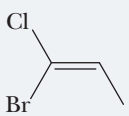
(b) Groups of higher priority on carbons 2 and 3 are —Cl and —CH_2CH_3. Because these groups are on opposite sides of the double bond, the configuration of this alkene is E, and its name is (*E*)-2-chloro-2-pentene.

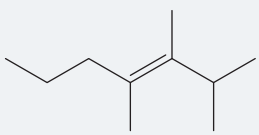
See problems 4.23, 4.27, 4.28, 4.32

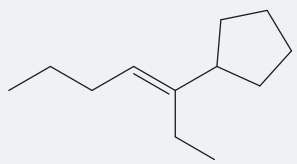
PROBLEM 4.3

Name each alkene and specify its configuration by the E,Z system:

(a) 

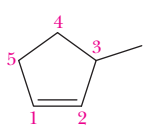
(b) 

(c) 

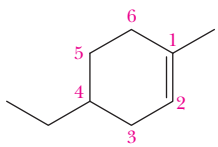
(d) 

D. Naming Cycloalkenes

In naming **cycloalkenes**, we number the carbon atoms of the ring double bond 1 and 2 in the direction that gives the substituent encountered first the smaller number. We name and locate substituents and list them in alphabetical order, as in the following compounds:



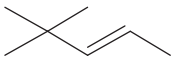
3-Methylcyclopentene (not 5-methylcyclopentene)



4-Ethyl-1-methylcyclohexene (not 5-ethyl-2-methylcyclohexene)

HOW TO 4.1 Name an Alkene

As an example of how to name an alkene, consider the following alkene, drawn here as a line-angle formula.



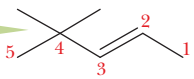
1. *Determine the parent chain, that is, the longest chain of carbon atoms that contains the functional group.*

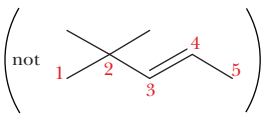
   In this example, the parent chain is five carbon atoms, making the compound a disubstituted pentene.

2. *Number the parent chain from the end that gives the carbon atoms of the double bond the lower set of numbers.*

   In this example, the parent chain is a disubstituted 2-pentene.

when numbering an alkene, give the C═C bond priority over any alkyl substituents





3. *Name and locate the substituents on the parent chain.*

   There are two methyl substituents on carbon 4 of the parent chain, and they are named 4,4-dimethyl-. The name to this point is 4,4-dimethyl-2-pentene.

4. *Determine whether the molecule shows* cis–trans *isomerism. If it does, use either the* cis–trans *or the E,Z system to specify the configuration.*

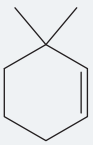
   In this example, the molecule shows *cis–trans* isomerism, and the double bond has the *trans* configuration. Therefore, the IUPAC name is *trans*-4,4-dimethyl-2-pentene.

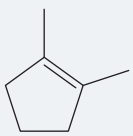
   Note that the double bond locator may be placed either before the parent name, as in the name just given, or immediately before the infix specifying the double bond to give the name *trans*-4,4-dimethylpent-2-ene.

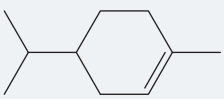
***trans*-4,4-Dimethyl-2-pentene**
or
***trans*-4,4-Dimethylpent-2-ene**
or
***(E)*-4,4-Dimethyl-2-pentene**

EXAMPLE 4.5

Write the IUPAC name for each cycloalkene:

(a) 

(b) 

(c) 

STRATEGY

The parent name of a cycloalkene is derived from the name of the alkene with the same number of carbon atoms (e.g., for a 6-carbon cycloalkene, use "cyclohexene" as the parent name). Number the carbon atoms of the ring 1 and 2 in the direction that gives the substituent encountered first the smaller number. Finally, name and number all substituents and list them in alphabetical order.

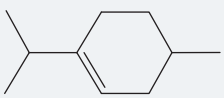
SOLUTION

(a) 3,3-Dimethylcyclohexene
(b) 1,2-Dimethylcyclopentene
(c) 4-Isopropyl-1-methylcyclohexene

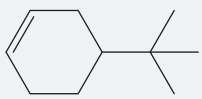
See problems 4.15–4.20

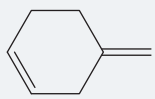
PROBLEM 4.4

Write the IUPAC name for each cycloalkene:

(a) 

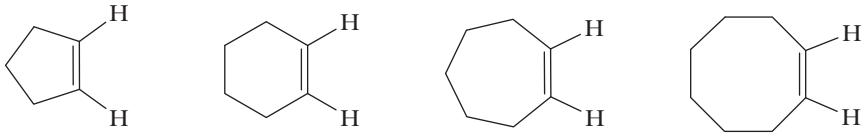
(b) 

(c) 

(d) 

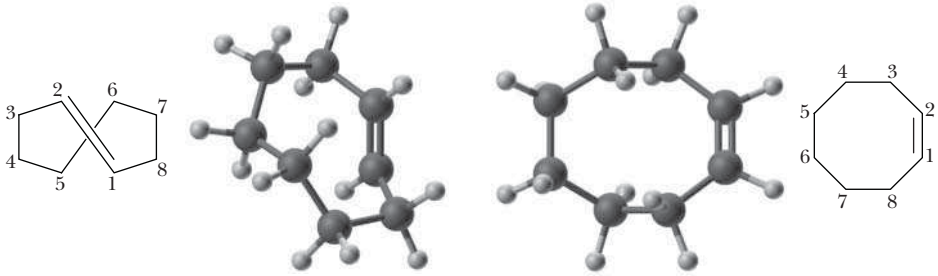
E. *Cis–Trans* Isomerism in Cycloalkenes

Following are structural formulas for four cycloalkenes:



Cyclopentene Cyclohexene Cycloheptene Cyclooctene

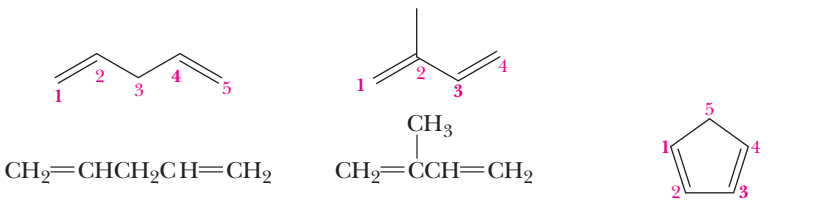
In these representations, the configuration about each double bond is *cis*. Because of angle strain, it is not possible to have a *trans* configuration in cycloalkenes of seven or fewer carbons. To date, *trans*-cyclooctene is the smallest *trans*-cycloalkene that has been prepared in pure form and is stable at room temperature. Yet, even in this *trans*-cycloalkene, there is considerable intramolecular strain. *cis*-Cyclooctene is more stable than its *trans* isomer by 38 kJ/mol (9.1 kcal/mol).



trans-Cyclooctene *cis*-Cyclooctene

F. Dienes, Trienes, and Polyenes

We name alkenes that contain more than one double bond as alkadienes, alkatrienes, and so forth. We refer to those that contain several double bonds more generally as polyenes (Greek: *poly*, many). Following are three examples of dienes:



1,4-Pentadiene 2-Methyl-1,3-butadiene (Isoprene) 1,3-Cyclopentadiene

G. *Cis–Trans* Isomerism in Dienes, Trienes, and Polyenes

Thus far, we have considered *cis–trans* isomerism in alkenes containing only one carbon–carbon double bond. For an alkene with one carbon–carbon double bond that can show *cis–trans* isomerism, two *cis–trans* isomers are possible. For an alkene with ***n*** carbon–carbon double bonds, each of which can show *cis–trans* isomerism, $\mathbf{2^n}$ *cis–trans* isomers are possible.

EXAMPLE 4.6

How many *cis–trans* isomers are possible for 2,4-heptadiene?

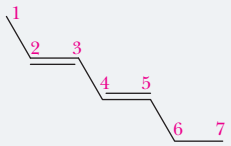
STRATEGY

Determine which of the carbon–carbon double bonds can show *cis–trans* isomerism. The number of *cis–trans* isomers possible is 2^n. *n* is the number of double bonds that may exhibit this type of isomerism.

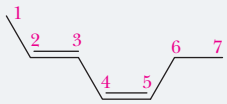
SOLUTION

This molecule has two carbon–carbon double bonds, each of which exhibits *cis–trans* isomerism. As the following table shows, $2^2 = 4$ *cis–trans* isomers are possible (below the table are line-angle formulas for two of these isomers):

Double bond	
$C_2—C_3$	$C_4—C_5$
trans	*trans*
trans	*cis*
cis	*trans*
cis	*cis*



trans,trans-2,4-Heptadiene



trans,cis-2,4-Heptadiene

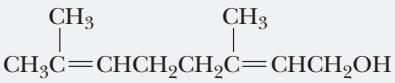
See problem 4.36

PROBLEM 4.5

Draw structural formulas for the other two *cis–trans* isomers of 2,4-heptadiene.

EXAMPLE 4.7

Draw all possible *E-Z* isomers for the following unsaturated alcohol:

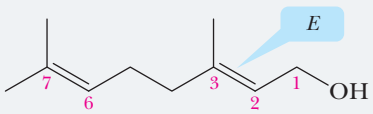


STRATEGY

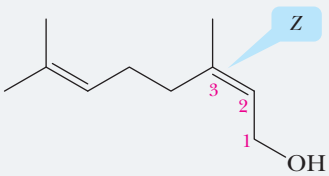
Identify the number of C–C double bonds, *n*, that exhibit *E-Z* isomerism. The number of possible *E-Z* isomers will then be equal to 2^n. Alkene carbons that are bonded to two identical groups do not exhibit *E-Z* isomerism.

SOLUTION

E-Z isomerism is possible only for the double bond between carbons 2 and 3 of the chain. It is not possible for the other double bond because carbon 7 has two identical groups on it. Thus, $2^1 = 2$ *E-Z* isomers are possible.



The *E* isomer



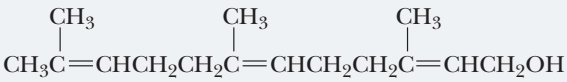
The *Z* isomer

The *E* isomer of this alcohol, named geraniol, is a major component of the oils of rose, citronella, and lemongrass.

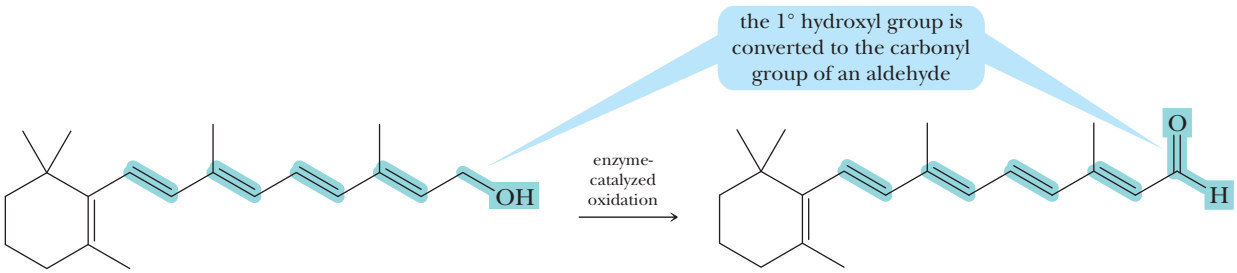
See problem 4.36

PROBLEM 4.6

How many *E-Z* isomers are possible for the following unsaturated alcohol?



Vitamin A is an example of a biologically important compound for which a number of *E-Z* isomers are possible. There are four carbon–carbon double bonds in the chain of carbon atoms bonded to the substituted cyclohexene ring, and each has the potential for *E-Z* isomerism. Thus, $2^4 = 16$ *E-Z* isomers are possible for this structural formula. Vitamin A is the all *E* isomer. The enzyme-catalyzed oxidation of vitamin A converts the primary hydroxyl group to a carbonyl group of an aldehyde to give retinal, the biologically active form of the vitamin:

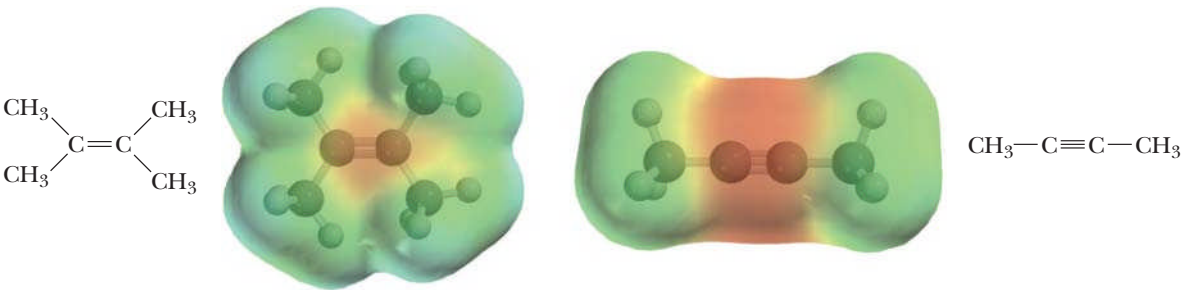


Vitamin A (retinol)

Vitamin A aldehyde (retinal)

4.3 What Are the Physical Properties of Alkenes and Alkynes?

Alkenes and alkynes are nonpolar compounds, and the only attractive forces between their molecules are dispersion forces (Section 3.8B). Therefore, their physical properties are similar to those of alkanes (Section 3.8) with the same carbon skeletons. Alkenes and alkynes that are liquid at room temperature have densities less than 1.0 g/mL. Thus, they are less dense than water. Like alkanes, alkenes and alkynes are nonpolar and are soluble in each other. Because of their contrasting polarity with water, they do not dissolve in water. Instead, they form two layers when mixed with water or another polar organic liquid such as ethanol.



Tetramethylethylene and dimethylacetylene. Both a carbon–carbon double bond and a carbon–carbon triple bond are sites of high electron density and, therefore, sites of chemical reactivity.

EXAMPLE 4.8

Describe what will happen when 1-nonene is added to the following compounds:

(a) Water
(b) 8-Methyl-1-nonyne

STRATEGY

First determine the polarity of the solvent and the solute. Then apply the generalization, "like dissolves like."

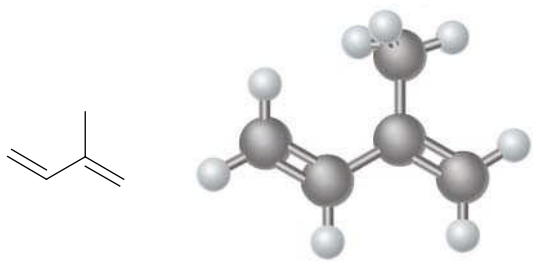
SOLUTION

(a) 1-Nonene is an alkene and, therefore, nonpolar. It will not dissolve in a polar solvent such as water. Water and 1-nonene will form two layers; water, which has the higher density, will be the lower layer, and 1-nonene will be the upper layer.
(b) Because alkenes and alkynes are both nonpolar, they will dissolve in one another.

Chemical Connections 4C

WHY PLANTS EMIT ISOPRENE

Names like Virginia's *Blue Ridge*, Jamaica's *Blue Mountain Peak*, and Australia's *Blue Mountains* remind us of the bluish haze that hangs over wooded hills in the summertime. In the 1950s, it was discovered that this haze is rich in isoprene, which means that isoprene is far more abundant in the atmosphere than anyone thought. The haze is caused by the scattering of light from an aerosol produced by the photooxidation of isoprene and other hydrocarbons. Scientists now estimate that the global emission of isoprene by plants is 3×10^{11} kg/yr (3.3×10^{8} ton/yr), which represents approximately 2% of all carbon fixed by photosynthesis.



Isoprene

A recent study of hydrocarbon emissions in the Atlanta area revealed that plants are by far the largest emitters of hydrocarbons, with plant-derived isoprene accounting for almost 60% of the total.

Digital Vision

The haze of the Smoky Mountains is caused by light-scattering from the aerosol produced by the photooxidation of isoprene and other hydrocarbons.

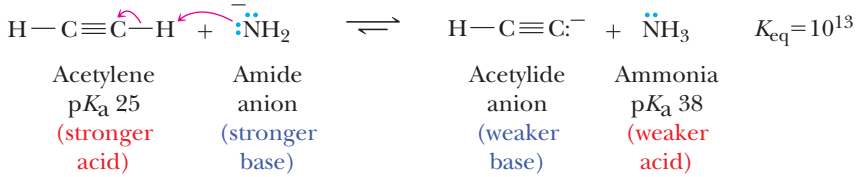
Why do plants emit so much isoprene into the atmosphere rather than use it for the synthesis of a variety of natural products? Tom Starkey, a University of Wisconsin plant physiologist, found that the emission of isoprene is extremely sensitive to temperature. Plants grown at 20 °C do not emit isoprene, but they begin to emit it when the temperature of their leaves increases to 30 °C. In certain plants, isoprene emission can increase as much as tenfold for a 10 °C increase in leaf temperature. Starkey studied the relationship between temperature-induced leaf damage and isoprene concentration in leaves of the kudzu plant, a non-native invasive vine. He discovered that leaf damage, as measured by the destruction of chlorophyll, begins to occur at 37.5 °C in the absence of isoprene, but not until 45 °C in its presence. Starkey speculates that isoprene dissolves in leaf membranes and in some way increases their tolerance to heat stress. Because isoprene is made rapidly and is also lost rapidly, its concentration correlates with temperature throughout the day.

Question

Based on the information in this Chemical Connections what can you deduce about the physical properties of leaf cell membranes?

4.4 Why Are 1-Alkynes (Terminal Alkynes) Weak Acids?

One of the major differences between the chemistry of alkynes and that of alkenes and alkanes is that a hydrogen bonded to a carbon atom of a terminal alkyne is sufficiently acidic (pK_a 25) that it can be removed by a strong base, such as sodium amide, $NaNH_2$, to give an acetylide anion.



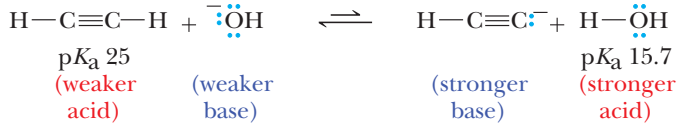
In this equilibrium, acetylene is the stronger acid and sodium amide is the stronger base, and the position of equilibrium lies considerably toward the right and favors formation of the acetylide anion and ammonia (Section 2.4). Table 4.1 gives pK_a values for an alkane, alkene, and an alkyne hydrogen. Also given for comparison is the value for water.

TABLE 4.1 Acidity of Alkanes, Alkenes, and Alkynes

Weak Acid		Conjugate Base	p*Ka*
Water	HO—H	HO^-	15.7
Alkyne	HC≡C—H	$HC{\equiv}C^-$	25
Alkene	$CH_2{=}CH{-}H$	$CH_2{=}CH^-$	44
Alkane	$CH_3CH_2{-}H$	$CH_3CH_2^-$	51

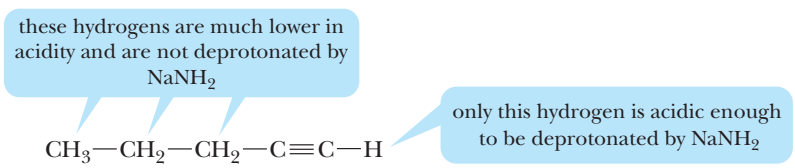
Increasing acidity

Because water (pK_a 15.7) is a stronger acid than acetylene (pK_a 25), the hydroxide ion is not a strong enough base to convert a terminal alkyne to an alkyne anion. The position of equilibrium for this acid–base reaction lies toward the left.



The pK_a values for alkene hydrogens (pK_a approximately 44) and alkane hydrogens (pK_a approximately 51) are so large (they are so weakly acidic) that neither the commonly used alkali metal hydroxides nor sodium amide are strong enough bases to remove a proton from an alkene or an alkane.

Why is the acidity of a hydrogen bonded to a triple-bonded carbon so much more acidic than one bonded to a double-bonded carbon of an alkene or to an alkane? We explain these relative acidities in the following way. The lone pair of electrons on a carbon anion lies in a hybrid orbital: an sp^3 hybrid orbital for an alkane, an sp^2 hybrid orbital for an alkene, and an sp hybrid orbital for an alkyne. An sp hybrid orbital has 50% s character, an sp^2 hybrid orbital has 33% s character, and an sp^3 hybrid orbital has 25% s character. Recall from your course in general chemistry and from Chapter 1 of this text that a 2s orbital is lower in energy than a 2p orbital. Consequently, electrons in a 2s orbital are held more tightly to the nucleus than those in a 2p orbital. The more s character in a hybrid orbital of carbon, the more electronegative the carbon atom will be, resulting in a greater stability of the anion and thus a more acidic hydrogen. Of the three types of organic compounds in the series alkyne, alkene, and alkane, the carbon in an alkyne (sp hybridized with 50% s character) is the most electronegative. Therefore, an alkyne anion is the most stable of the series, and an alkyne is the strongest acid of the series. By similar reasoning, the alkane carbon (sp^3 hybridized and 25% s character) is the least electronegative, and an alkane is the weakest acid of the series. An alkene, with 33% s character, is intermediate. Finally, it is only the hydrogen of a 1-alkyne that shows this type of acidity. No other hydrogens of an alkyne have comparable acidity, and no other hydrogens are removed by $NaNH_2$.



SUMMARY OF KEY QUESTIONS

4.1 What Are the Structures and Shapes of Alkenes and Alkynes?

- An **alkene** is an **unsaturated hydrocarbon** that contains a carbon–carbon double bond.
- Alkenes have the general formula C_nH_{2n}.
- An **alkyne** is an unsaturated hydrocarbon that contains a carbon–carbon triple bond.
- Alkynes have the general formula C_nH_{2n-2}.
- According to the **orbital overlap model**, a carbon–carbon double bond consists of one sigma bond formed by the overlap of sp^2 hybrid orbitals and one pi bond formed by the overlap of parallel 2p atomic orbitals. It takes approximately 264 kJ/mol (63 kcal/mol) to break the pi bond in ethylene.
- A carbon–carbon triple bond consists of one sigma bond formed by the overlap of sp hybrid orbitals and two pi bonds formed by the overlap of pairs of parallel 2p orbitals.
- The structural feature that makes **cis–trans isomerism** possible in alkenes is restricted rotation about the two carbons of the double bond.
- To date, *trans*-cyclooctene is the smallest *trans*-cycloalkene that has been prepared in pure form and is stable at room temperature.

4.2 How Do We Name Alkenes and Alkynes?

- According to the IUPAC system, we show the presence of a **carbon–carbon double bond** by changing the infix of the parent hydrocarbon from **-an-** to **-en-**.

- The names *vinyl* and *allyl* are commonly used to show the presence of $-CH=CH_2$ and $-CH_2CH=CH_2$ groups.
- We show the presence of a **carbon–carbon triple bond** by changing the infix of the parent alkane from **-an-** to **-yn-**.
- The orientation of the carbon atoms of the parent chain about the double bond determines whether an alkene is *cis* or *trans*. If atoms of the parent are on the same side of the double bond, the configuration of the alkene is *cis*; if they are on opposite sides, the configuration is *trans*.
- Using a set of priority rules, we can also specify the configuration of a carbon–carbon double bond by the **E,Z system**.
- If the two groups of higher priority are on the same side of the double bond, the configuration of the alkene is **Z** (German: *zusammen*, together); if they are on opposite sides, the configuration is **E** (German: *entgegen*, opposite).
- To name an alkene containing two or more double bonds, we change the infix to -adien-, -atrien-, and so forth. Compounds containing several double bonds are called polyenes.

4.3 What Are the Physical Properties of Alkenes and Alkynes?

- Alkenes and alkynes are nonpolar compounds, and the only interactions between their molecules are **dispersion forces**.
- The physical properties of alkenes and alkynes are similar to those of alkanes.

4.4 Why Are 1-Alkynes (Terminal Alkynes) Weak Acids?

- Terminal alkynes are weakly acidic (pK_a 25) and can be converted to alkyne anions by strong bases such as sodium amide, $NaNH_2$.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Ethylene and acetylene are constitutional isomers. (4.2)
2. Alkanes that are liquid at room temperature are insoluble in water and when added to water will float on water. (4.3)
3. The bulk of the ethylene used by the chemical industry worldwide is obtained from nonrenewable resources. (4.1)
4. Alkenes and alkynes are nonpolar molecules. (4.3)
5. The IUPAC name of $CH_3CH=CHCH_3$ is 1,2-dimethylethylene. (4.2)
6. Cyclohexane and 1-hexene are constitutional isomers. (4.1)
7. The IUPAC name of an alkene is derived from the name of the longest chain of carbon atoms that contains the double bond. (4.2)
8. There are two classes of unsaturated hydrocarbons, alkenes and alkynes. (4.1)
9. Both geraniol and menthol (pp. 243–244) show *cis–trans* isomerism. (4.4)
10. 1,2-Dimethylcyclohexene shows *cis–trans* isomerism. (4.2)
11. 2-Methyl-2-butene shows *cis–trans* isomerism. (4.2)
12. Both ethylene and acetylene are planar molecules. (4.1)
13. The physical properties of alkenes are similar to those of alkanes with the same carbon skeletons. (4.3)
14. Isoprene is the common name for 2-methyl-1,3-butadiene. (4.4)

Answers: (1) F (2) T (3) T (4) T (5) F (6) T (7) T (8) F (9) T (10) F (11) F (12) T (13) T (14) T

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 4.1 Structure of Alkenes and Alkynes

4.7 Describe what will happen when *trans*-3-heptene is added to the following compounds:

(a) Cyclohexane (b) Ammonia (*l*)

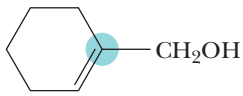
4.8 Each carbon atom in ethane and in ethylene is surrounded by eight valence electrons and has four bonds to it. Explain how VSEPR (Section 1.3) predicts a bond angle of 109.5° about each carbon in ethane, but an angle of 120° about each carbon in ethylene.

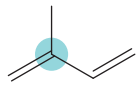
4.9 Explain the difference between saturated and unsaturated.

4.10 Use valence-shell electron-pair repulsion (VSEPR) to predict all bond angles about each of the following highlighted carbon atoms.

(a) 

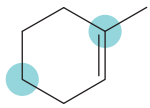
(c) 

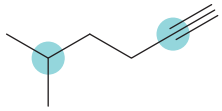
(b) 

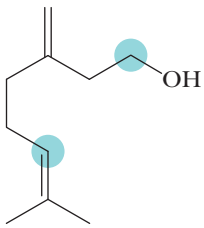
(d) 

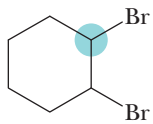
4.11 For each highlighted carbon atom in Problem 4.10, identify which orbitals are used to form each sigma bond and which are used to form each pi bond.

4.12 Predict all bond angles about each highlighted carbon atom:

(a) 

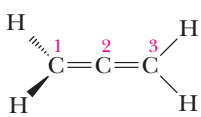
(c) 

(b) 

(d) 

4.13 For each highlighted carbon atom in Problem 4.12, identify which orbitals are used to form each sigma bond and which are used to form each pi bond.

4.14 Following is the structure of 1,2-propadiene (allene). In it, the plane created by H—C—H of carbon 1 is perpendicular to that created by H—C—H of carbon 3.



1,2-Propadiene (Allene)

Ball-and-stick model

(a) State the orbital hybridization of each carbon in allene.

(b) Account for the molecular geometry of allene in terms of the orbital overlap model. Specifically, explain why all four hydrogen atoms are not in the same plane.

SECTION 4.2 Nomenclature of Alkenes and Alkynes

4.15 Draw a structural formula for each compound: **(See Examples 4.1, 4.5)**

(a) *trans*-2-Methyl-3-hexene

(b) 2-Methyl-3-hexyne

(c) 2-Methyl-1-butene

(d) 3-Ethyl-3-methyl-1-pentyne

(e) 2,3-Dimethyl-2-butene

(f) *cis*-2-Pentene

(g) (*Z*)-1-Chloropropene

(h) 3-Methylcyclohexene

4.16 Draw a structural formula for each compound: **(See Examples 4.1, 4.5)**

(a) 1-Isopropyl-4-methylcyclohexene

(b) (6*E*)-2,6-Dimethyl-2,6-octadiene

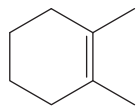
(c) *trans*-1,2-Diisopropylcyclopropane

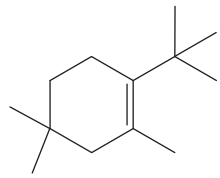
(d) 2-Methyl-3-hexyne

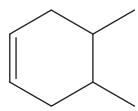
(e) 2-Chloropropene

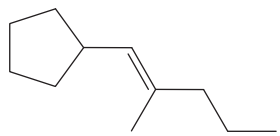
(f) Tetrachloroethylene

4.17 Write the IUPAC name for each compound: **(See Examples 4.1, 4.5)**

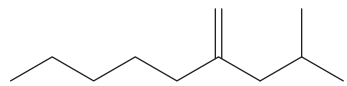
(a) 

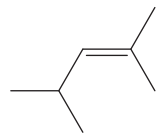
(c) 

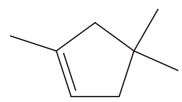
(b) 

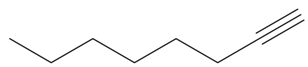
(d) 

4.18 Write the IUPAC name for each compound: **(See Examples 4.1, 4.5)**

(a) 

(e) 

(b) 

(f) 

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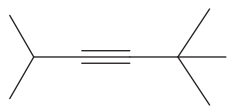
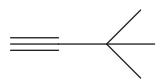
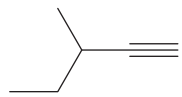
(g) 

(d) 

(h) 

4.19 Explain why each name is incorrect, and then write a correct name for the intended compound: **(See Examples 4.1, 4.5)**

(a) 1-Methylpropene

(b) 3-Pentene

(c) 2-Methylcyclohexene

(d) 3,3-Dimethylpentene

(e) 4-Hexyne

(f) 2-Isopropyl-2-butene

4.20 Explain why each name is incorrect, and then write a correct name for the intended compound: **(See Examples 4.1, 4.5)**

(a) 2-Ethyl-1-propene

(b) 5-Isopropylcyclohexene

(c) 4-Methyl-4-hexene

(d) 2-*sec*-Butyl-1-butene

(e) 6,6-Dimethylcyclohexene

(f) 2-Ethyl-2-hexene

SECTIONS 4.2 AND 4.3 *Cis–Trans* (E/Z) Isomerism in Alkenes and Cycloalkenes

4.21 Which of these alkenes show *cis–trans* isomerism? For each that does, draw structural formulas for both isomers. **(See Example 4.2)**

(a) 1-Hexene
(b) 2-Hexene
(c) 3-Hexene
(d) 2-Methyl-2-hexene
(e) 3-Methyl-2-hexene
(f) 2,3-Dimethyl-2-hexene

4.22 Which of these alkenes show *cis–trans* isomerism? For each that does, draw structural formulas for both isomers. **(See Example 4.2)**

(a) 1-Pentene
(b) 2-Pentene
(c) 3-Ethyl-2-pentene
(d) 2,3-Dimethyl-2-pentene
(e) 2-Methyl-2-pentene
(f) 2,4-Dimethyl-2-pentene

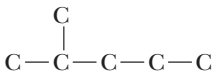
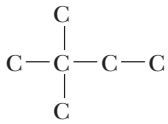
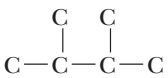
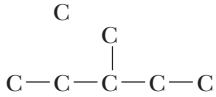
4.23 Which alkenes can exist as pairs of E/Z isomers? For each alkene that does, draw both isomers. **(See Examples 4.3, 4.4)**

(a) $CH_2{=}CHBr$
(b) $CH_3CH{=}CHBr$
(c) $(CH_3)_2C{=}CHCH_3$
(d) $(CH_3)_2CHCH{=}CHCH_3$

4.24 There are three compounds with the molecular formula $C_2H_2Br_2$. Two of these compounds have a dipole greater than zero, and one has no dipole. Draw structural formulas for the three compounds, and explain why two have dipole moments but the third one has none.

4.25 Name and draw structural formulas for all alkenes with the molecular formula C_5H_{10}. As you draw these alkenes, remember that *cis* and *trans* isomers are different compounds and must be counted separately.

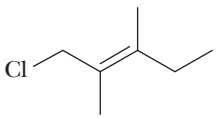
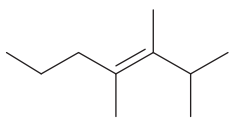
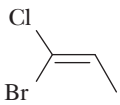
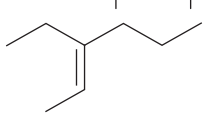
4.26 Name and draw structural formulas for all alkenes with the molecular formula C_6H_{12} that have the following carbon skeletons (remember *cis* and *trans* isomers):

(a) 
(c) 
(b) 
(d) 

4.27 Arrange the groups in each set in order of increasing priority: **(See Examples 4.3, 4.4)**

(a) $-CH_3$, $-Br$, $-CH_2CH_3$
(b) $-OCH_3$, $-CH(CH_3)_2$, $-CH_2CH_2NH_2$
(c) $-CH_2OH$, $-COOH$, $-OH$
(d) $-CH{=}CH_2$, $-CH{=}O$, $-CH(CH_3)_2$

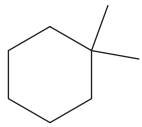
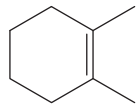
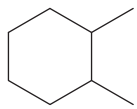
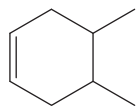
4.28 Name each alkene and specify its configuration using the E,Z system. **(See Examples 4.3, 4.4)**

(a) 
(c) 
(b) 
(d) 

4.29 Draw the structural formula for at least one bromoalkene with molecular formula C_5H_9Br that **(a)** shows E,Z isomerism and **(b)** does not show E,Z isomerism.

4.30 Is *cis–trans* isomerism possible in alkanes? Is it possible in alkynes? Explain.

4.31 For each molecule that shows *cis–trans* isomerism, draw the *cis* isomer:

(a) 
(c) 
(b) 
(d) 

4.32 Explain why each name is incorrect or incomplete, and then write a correct name: **(See Examples 4.3, 4.4)**

(a) (*Z*)-2-Methyl-1-pentene
(b) (*E*)-3,4-Diethyl-3-hexene
(c) *trans*-2,3-Dimethyl-2-hexene
(d) (1*Z*,3*Z*)-2,3-Dimethyl-1,3-butadiene

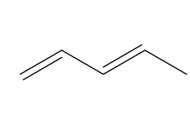
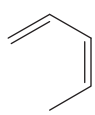
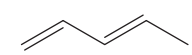
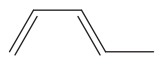
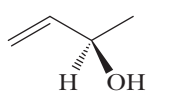
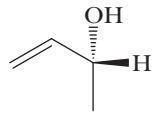
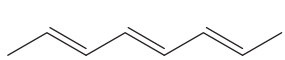
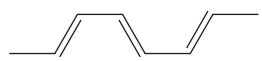
4.33 Draw structural formulas for all compounds with the molecular formula C_5H_{10} that are

(a) Alkenes that do not show *cis–trans* isomerism.
(b) Alkenes that do show *cis–trans* isomerism.
(c) Cycloalkanes that do not show *cis–trans* isomerism.
(d) Cycloalkanes that do show *cis–trans* isomerism.

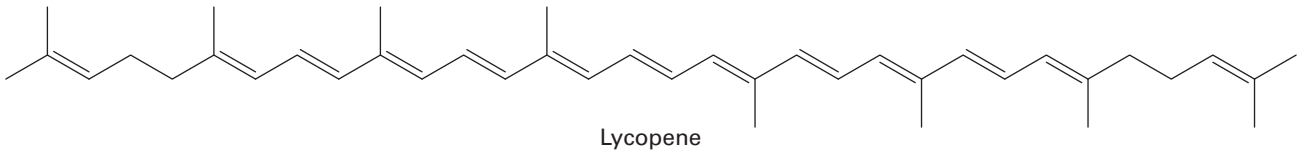
***4.34** β-Ocimene, a triene found in the fragrance of cotton blossoms and several essential oils, has the IUPAC name (3*Z*)-3,7-dimethyl-1,3,6-octatriene. Draw a structural formula for β-ocimene.

***4.35** Oleic acid and elaidic acid are, respectively, the *cis* and *trans* isomers of 9-octadecenoic acid. One of these fatty acids, a colorless liquid that solidifies at 4°C, is a major component of butterfat. The other, a white solid with a melting point of 44–45°C, is a major component of partially hydrogenated vegetable oils. Which of these two fatty acids is the *cis* isomer and which is the *trans* isomer? (*Hint*: Think about the geometry of packing and the relative strengths of the resulting dispersion forces.)

4.36 Determine whether the structures in each set represent the same molecule, *cis–trans* isomers, or constitutional isomers. If they are the same molecule, determine whether they are in the same or different conformations as a result of rotation about a carbon–carbon single bond. **(See Examples 4.6, 4.7)**

(a)  and 
(b)  and 
(c)  and 
(d)  and 

***4.37** Following is the structural formula of lycopene, a deep-red compound that is partially responsible for the red color of ripe fruits, especially tomatoes:



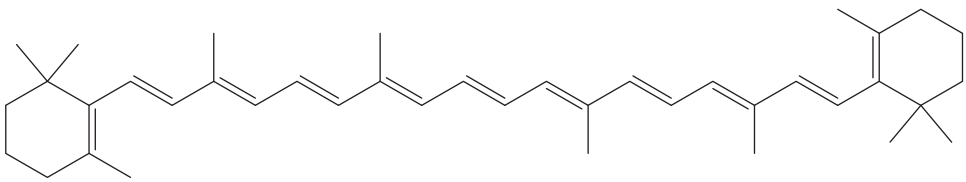
Lycopene

Approximately 20 mg of lycopene can be isolated from 1 kg of fresh, ripe tomatoes. How many of the carbon–carbon double bonds in lycopene have the possibility for *E-Z* isomerism? Use the E, Z system to assign the configuration of all applicable double bonds.

***4.38** As you might suspect, β-carotene, a precursor of vitamin A, was first isolated from carrots. Dilute solutions of β-carotene are yellow—hence its use as a food coloring. In plants, it is almost always present in combination with chlorophyll to assist in harvesting the energy of sunlight. As tree leaves die in the fall, the green of their chlorophyll molecules is replaced by the yellows and reds of carotene and carotene-related molecules.

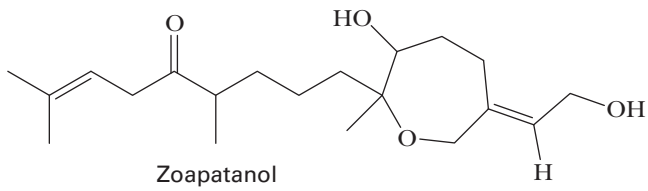
(a) Compare the carbon skeletons of β-carotene and lycopene. What are the similarities? What are the differences?

(b) Use the E,Z system to assign the configuration of all applicable double bonds.



β-Carotene

***4.39** In many parts of South America, extracts of the leaves and twigs of *Montanoa tomentosa* are used as a contraceptive, to stimulate menstruation, to facilitate labor, and as an abortifacient. The compound responsible for these effects is zoapatanol:



Zoapatanol

(a) Specify the configuration about the carbon–carbon double bond to the seven-membered ring, according to the E,Z system.

(b) How many *cis–trans* isomers are possible for zoapatanol? Consider the possibilities for *cis–trans* isomerism in cyclic compounds and about carbon–carbon double bonds.

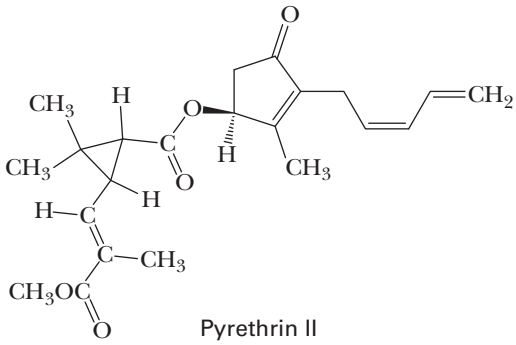
***4.40** Pyrethrin II and pyrethrosin are natural products isolated from plants of the chrysanthemum family:

Chrysanthemum blossoms.

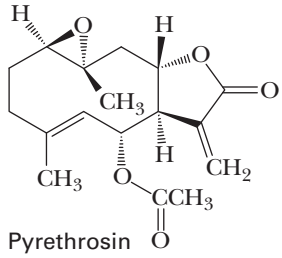
Pyrethrin II is a natural insecticide and is marketed as such.

(a) Label all carbon–carbon double bonds in each about which *cis–trans* isomerism is possible.

(b) Why are *cis–trans* isomers possible about the three-membered ring in pyrethrin II, but not about its five-membered ring?



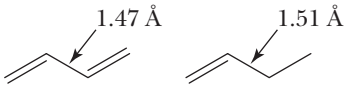
Pyrethrin II



Pyrethrosin

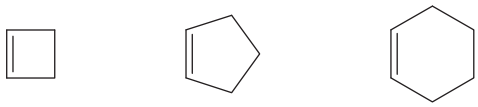
LOOKING AHEAD

4.41 Explain why the central carbon–carbon single bond in 1,3-butadiene is slightly shorter than the central carbon–carbon single bond in 1-butene:

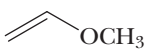
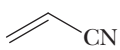


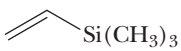
1,3-Butadiene 1-Butene

4.42 What effect might the ring size in the following cycloalkenes have on the reactivity of the C═C double bond in each?



4.43 What effect might each substituent have on the electron density surrounding the alkene C═C bond; that is, how does each substituent affect whether each carbon of the C—C double bond is partially positive or partially negative?

(a)  (b) 

(c) 

***4.44** In Section 19.1 on the biochemistry of fatty acids, we will study the following three long-chain unsaturated carboxylic acids:

$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$

Oleic acid

$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$

Linolenic acid

$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$

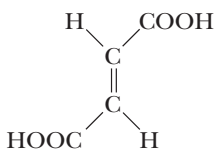
Linolenic acid

Each has 18 carbons and is a component of animal fats, vegetable oils, and biological membranes. Because of their presence in animal fats, they are called fatty acids.

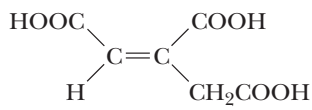
(a) How many *E-Z* isomers are possible for each fatty acid?

(b) These three fatty acids occur in biological membranes almost exclusively in the *cis* configuration. Draw line-angle formulas for each fatty acid, showing the *cis* configuration about each carbon–carbon double bond.

***4.45** Assign an E or a Z configuration or a *cis* or a *trans* configuration to these carboxylic acids, each of which is an intermediate in the citric acid cycle. Under each is given its common name.

(a) 

Fumaric acid

(b) 

Aconitic acid

GROUP LEARNING ACTIVITIES

4.46 Take turns coming up with structures that fit the following criteria. For each structure you come up with, explain to the group why your answer is correct.

(a) An alkene with the formula C_6H_{12} that cannot be named using *cis–trans* or E,Z.

(b) A compound with the formula C_7H_{12} that does not contain a pi bond.

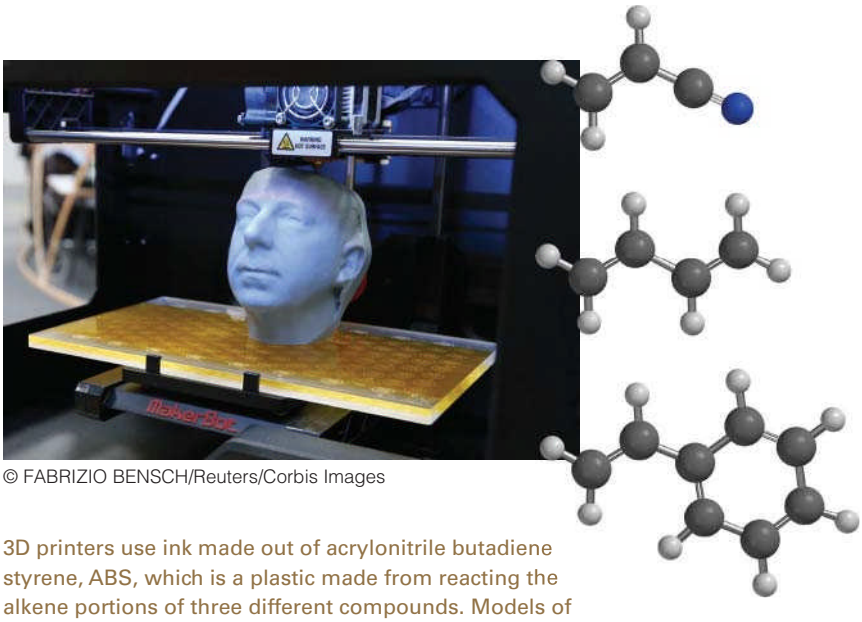
(c) A compound with the formula C_6H_{10} that does not contain a methylene group.

(d) An alkene that uses "vinyl" in its IUPAC name.

(e) A compound that can be named with the E,Z system but not with the *cis–trans* system.

(f) A compound that can be named with the *cis–trans* system but not with the E,Z system.

(g) A *trans*-cycloalkene that has no ring or angle strain. (*Hint*: You may need to use a model kit to explain.)



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3D printers use ink made out of acrylonitrile butadiene styrene, ABS, which is a plastic made from reacting the alkene portions of three different compounds. Models of acrylonitrile, 1,3-butadiene, and styrene.

Reactions of Alkenes and Alkynes

5

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

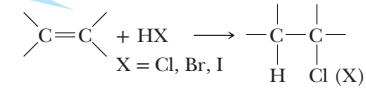
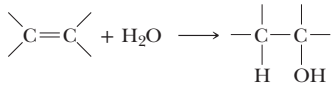
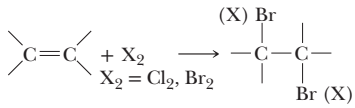
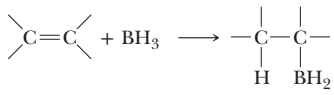
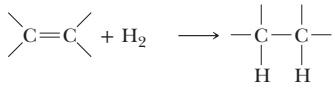
IN THE PREVIOUS CHAPTER, we learned about alkenes and alkynes, classes of hydrocarbons that contain a carbon–carbon pi bond. Why are carbon-carbon pi bonds so prevalent in organic chemistry? Why are they critical to so many biological and industrial processes? How do scientists take advantage of the special chemistry that they undergo? These questions will be answered in this chapter as we begin our systematic study of organic reactions and their reaction mechanisms. Reaction mechanisms are step-by-step descriptions of how reactions proceed and are one of the unifying concepts in organic chemistry. We will use the reactions of alkenes and alkynes as a vehicle to introduce this important concept.

5.1 What Are the Characteristic Reactions of Alkenes?

The most characteristic reaction of alkenes is **addition to the carbon–carbon double bond** in such a way that the pi bond is broken and, in its place, sigma bonds are formed to two new atoms or groups of atoms. Several examples of reactions at the carbon–carbon double bond are shown in Table 5.1, along with the descriptive name(s) associated with each.

From the perspective of the chemical industry, the single most important reaction of ethylene and other low-molecular-weight alkenes is the production of **chain-growth polymers** (Greek: *poly*, many, and *meros*, part). In the presence of certain catalysts called *initiators*, many

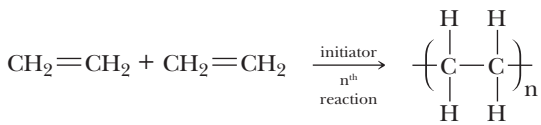
TABLE 5.1 Characteristic Reactions of Alkenes

Reaction	Descriptive Name(s)
	Hydrochlorination (hydrohalogenation)
	Hydration
	Bromination (halogenation)
	Hydroboration
	Hydrogenation (reduction)

in each reaction, the double bond has reacted such that a pi bond has been broken, and sigma bonds are formed to new atoms or groups of atoms on each carbon of the former pi bond

in Section 5.5, we will see how the —BH_2 group is replaced by an —OH group to give the desired product

alkenes form polymers by the addition of **monomers** (Greek: *mono*, one, and *meros*, part) to a growing polymer chain, as illustrated by the formation of polyethylene from ethylene:



polyethylene

In alkene polymers of industrial and commercial importance, n is a large number, typically several thousand. We discuss this alkene reaction in Chapter 16.

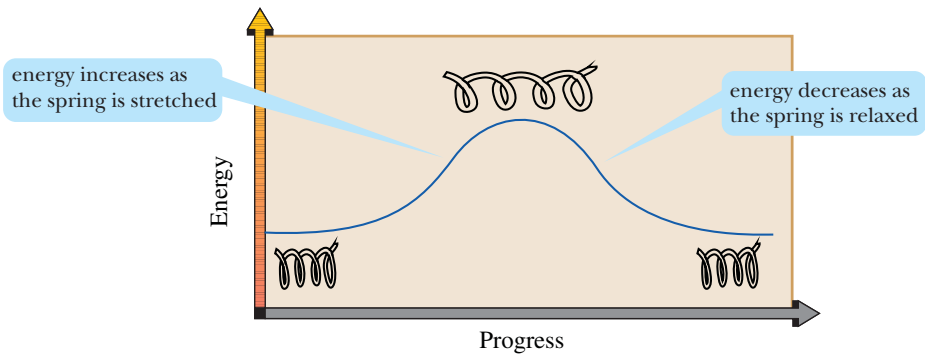
5.2 What Is a Reaction Mechanism?

Reaction mechanism A step-by-step description of how a chemical reaction occurs.

A **reaction mechanism** describes in detail how a chemical reaction occurs. It describes which bonds break and which new ones form, the order and relative rates of the various bond-breaking and bond-forming steps, the role of the solvent if the reaction takes place in solution, and the role of any catalysts. In addition to reaction mechanisms, chemists often use other tools to describe the various features of a chemical reaction. One such tool is the reaction energy diagram.

A. Energy Diagrams and Transition States

To understand the relationship between a chemical reaction and energy, think of a chemical bond as a spring. As a spring is stretched from its resting position, its energy increases and its two ends change position. As it returns to its resting position, its energy decreases. The entire process is represented as follows from start (left side of the graph) to finish (right side of the graph).



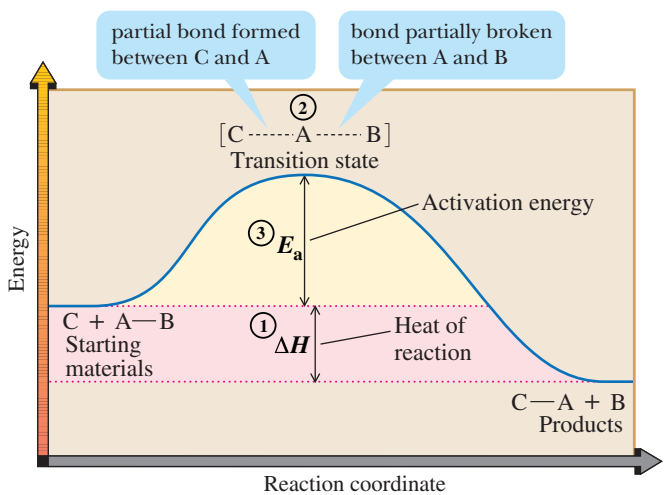
Similarly, during a chemical reaction, bond breaking corresponds to an increase in energy, and bond forming corresponds to a decrease in energy. As we did with the spring, we use an **energy diagram** to show the changes in energy that occur in going from reactants to products. Energy is measured along the vertical axis, and the change in position of the atoms during a reaction is measured on the horizontal axis, called the **reaction coordinate**. The reaction coordinate indicates how far the reaction has progressed, from no reaction to a completed reaction.

Refer to Figure 5.1 and its numbered features as we use an energy diagram to describe the reaction of C + A—B to form C—A + B. This reaction occurs in one step, meaning that bond breaking in reactants and bond forming in products occur simultaneously.

1. The difference in energy between the reactants and products is called the **heat of reaction**, ΔH. In this example, the energy of the products is lower than that of the reactants, heat is released and the reaction is **exothermic**. When the energy of the products is higher than that of the reactants, heat is absorbed and the reaction is called **endothermic**.

2. A **transition state** is the point on the reaction coordinate at which the energy is at a maximum. At the transition state, there is sufficient energy to cause the bonds in the reactants to break. As bonds break, energy is redistributed and new bonds form, giving products. Once the transition state is reached, the reaction proceeds to give products and energy is released. A transition state has a definite geometry, a definite arrangement of bonding and nonbonding electrons, and a definite distribution of electron density and charge. However, because a transition state is at an energy maximum on an energy diagram, we cannot isolate it and we cannot determine its structure experimentally. Its lifetime is on the order of a picosecond (the duration of a single bond vibration). As we will see, however, even though we cannot observe a transition state directly by any experimental means, we can often infer a great deal about its probable structure from other experimental observations.

3. The difference in energy between the reactants and the transition state is called the **activation energy**, E_a. The activation energy is the energy barrier for a reaction, the



Energy diagram A graph showing the changes in energy that occur during a chemical reaction; energy is plotted on the *y*-axis, and the progress of the reaction is plotted on the *x*-axis.

Reaction coordinate A measure of the progress of a reaction, plotted on the *x*-axis in an energy diagram.

Heat of reaction, ΔH The difference in energy between reactants and products.

Exothermic reaction A reaction in which the energy of the products is lower than the energy of the reactants; a reaction in which heat is liberated.

Endothermic reaction A reaction in which the energy of the products is higher than the energy of the reactants; a reaction in which heat is absorbed.

Transition state An unstable species of maximum energy formed during the course of a reaction; a maximum on an energy diagram.

Activation energy, E_a The difference in energy between reactants and the transition state.

FIGURE 5.1 An energy diagram for a one-step reaction between C and A—B. The dashed lines in the transition state indicate that the new C—A bond is partially formed and the A—B bond is partially broken. When the energy of the reactants is higher than that of the products, the reaction is exothermic.

minimum energy required for a reaction to occur, and it determines the rate of the reaction—that is, how fast the reaction occurs. When the activation energy is large, very few molecular collisions occur with sufficient energy to reach the transition state, and the reaction is slow. When the activation energy is small, many collisions generate sufficient energy to reach the transition state and the reaction is fast.

Reaction intermediate An unstable species that lies in an energy minimum between two transition states.

Rate-determining step The step in a reaction sequence that crosses the highest energy barrier; the slowest step in a multistep reaction.

In a reaction that occurs in two or more steps, each step has its own transition state and activation energy. Shown in Figure 5.2 is an energy diagram for the conversion of reactants to products in two steps. A **reaction intermediate** corresponds to an energy minimum between two transition states, in this case an intermediate between transition states 1 and 2. Because the energies of reaction intermediates are higher than the energies of either the reactants or the products, intermediates are highly reactive, and rarely, if ever, can one be isolated.

The slowest step in a multistep reaction, called the **rate-determining step**, is the step that crosses the highest energy barrier. In the two-step reaction shown in Figure 5.2, Step 1 crosses the higher energy barrier and is, therefore, the rate-determining step.

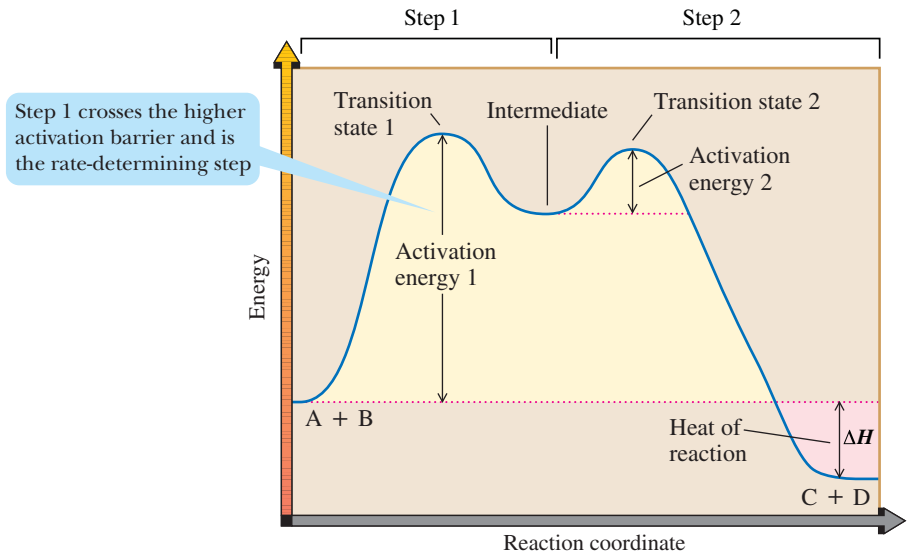


FIGURE 5.2 Energy diagram for a two-step reaction involving the formation of an intermediate. The energy of the reactants is higher than that of the products, and energy is released in the conversion of A + B to C + D.

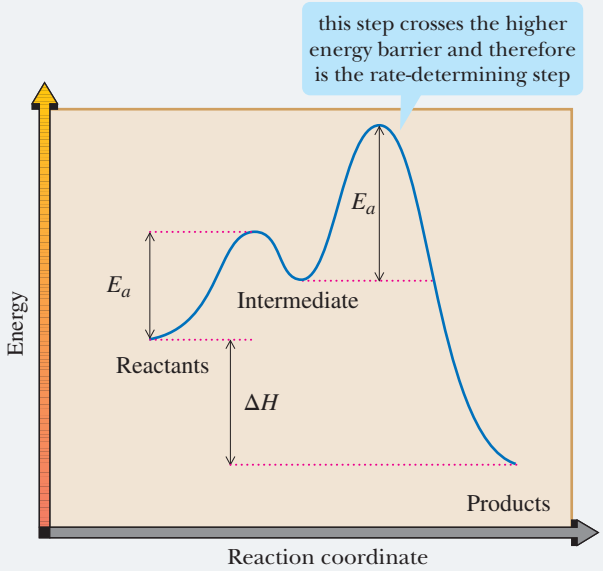
EXAMPLE 5.1

Draw an energy diagram for a two-step exothermic reaction in which the second step is rate determining.

STRATEGY

A two-step reaction involves the formation of an intermediate. In order for the reaction to be exothermic, the products must be lower in energy than the reactants. In order for the second step to be rate determining, it must cross the higher energy barrier.

SOLUTION



See problems 5.12, 5.13

PROBLEM 5.1

In what way would the energy diagram drawn in Example 5.1 change if the reaction were endothermic?

Chemical Connections 5A

CATALYTIC CRACKING AND THE IMPORTANCE OF ALKENES

By far, the largest source of hydrocarbons is crude oil, which contains mostly alkanes. This is unfortunate because, as we learned in Chapter 3, alkanes are relatively inert and would not be very useful as starting materials for organic reactions to produce the myriad of compounds used in society today.

Fortunately, crude oil is readily converted to alkenes, compounds with a reactive functional group (the C—C double bond), through the process of catalytic cracking. In catalytic cracking, the hydrocarbon feedstocks of crude oil are mixed with solid catalysts and heated to temperatures above 500°C. These conditions allow C—C single bonds to be broken, forming reactive intermediates that eventually react to form smaller alkanes and alkenes.

$$CH_3CH_2CH_2CH_2CH_2CH_3 \xrightarrow[\text{catalyst}]{\text{heat}} CH_3CH_2CH_2CH_3 + \underset{\text{ethylene}}{CH_2{=}CH_2}$$

The smaller hydrocarbons formed in the initial reactions react again to form even smaller hydrocarbons. After several cracking cycles, the major alkene product formed is ethylene, the smallest possible alkene.

$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{catalyst}]{\text{heat}} CH_3CH_3 + \underset{\text{ethylene}}{CH_2{=}CH_2}$$

$$CH_3CH_3 \xrightarrow[\text{catalyst}]{\text{heat}} H_2 + \underset{\text{ethylene}}{CH_2{=}CH_2}$$

The ethylene is then collected and subjected to other reactions, such as hydration to give ethanol.

$$CH_2{=}CH_2 \xrightarrow{\text{hydration}} \underset{\text{ethanol}}{CH_3CH_2OH}$$

Through this process, crude oil is converted to functionalized organic compounds which can, in turn, be used for many of the organic reactions presented in this text.

Question

Would you predict the catalytic cracking reactions to be exothermic or endothermic?

B. Developing a Reaction Mechanism

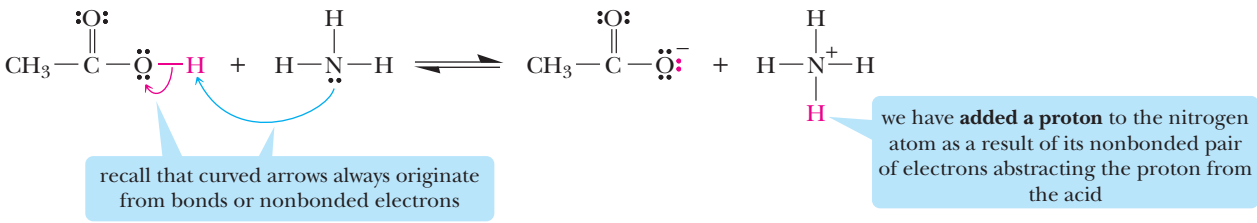
Chemists develop a reaction mechanism by designing experiments that will reveal details of a particular chemical reaction. Through a combination of experience and intuition, they propose one or more sets of steps or mechanisms, each of which might account for the overall chemical transformation. Finally, they test each proposed mechanism against the experimental observations to exclude those mechanisms that are not consistent with the facts. A mechanism becomes generally established by excluding reasonable alternatives and by showing that it is consistent with every test that can be devised. It is important to keep in mind that, as new experimental evidence is obtained, it may be necessary to modify a generally accepted mechanism or possibly even discard it and start all over again.

We might ask why it is worth the trouble to establish reaction mechanisms and to take the time to learn about them. One reason is very practical. Mechanisms provide a theoretical framework within which to organize a great deal of descriptive chemistry. For example, with insight into how reagents add to particular alkenes, it is possible to make generalizations and then predict how the same reagents might add to other alkenes. A second reason lies in the intellectual satisfaction derived from constructing models that accurately reflect the behavior of chemical systems. Finally, to a creative scientist, a mechanism is a tool to be used in the search for new knowledge and new understanding. A mechanism consistent with all that is known about a reaction can be used to make predictions about chemical interactions as yet unexplored, and experiments can be designed to test these predictions. Thus, reaction mechanisms provide a way not only to organize knowledge, but also to extend it.

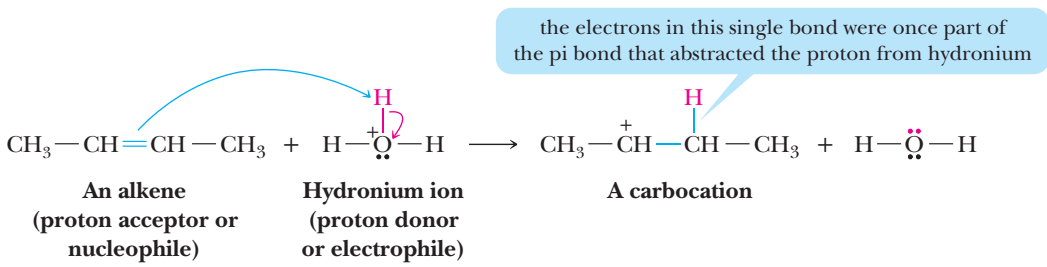
C. Some Common Patterns in Reaction Mechanisms

At this point, let us stop for a moment and analyze several of the common reaction mechanism patterns we will see in this and following chapters. Try to notice the sometimes subtle similarities and differences among the patterns, but do not worry if you cannot initially do so. Your ability to discern these patterns will grow as this course progresses.

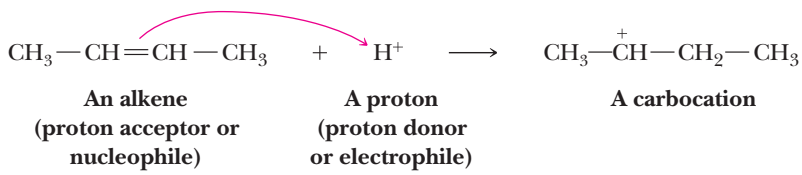
Pattern 1: Add a proton. In Section 2.2, we learned that an acid is a proton donor, a base is a proton acceptor, and an acid–base reaction is a proton-transfer reaction. In addition, we saw that we can use curved arrows to show how a proton-transfer reaction takes place, as for example, in the acid–base reaction between acetic acid and ammonia to form acetate ion and ammonium ion. This is an example of a *nonbonded pair of electrons being used to add a proton* to a compound.



Following is another example of **adding a proton**. Here, the *proton is added* across the pi bond of the C—C double bond. The compounds below are labeled as "proton donor" and "proton acceptor," terms used to describe Brønsted acids and bases. They can also be labeled according to Lewis acid–base theory as "electrophile" and "nucleophile."



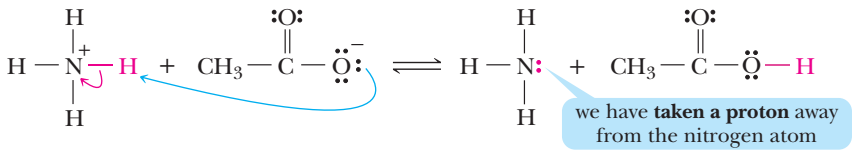
This pattern is typical in all reactions in which the reaction is catalyzed by an acid. Remember that in a carbon–carbon double bond, two pairs of electrons are shared between the two carbon atoms. An acid–base reaction in which a double bond provides the pair of electrons for the hydrogen transfer creates a carbocation. While the above equation is the most accurate way to write the proton transfer in aqueous solution, we will often simplify the equation to show just the proton and formation of the new covalent bond.



It is important to remember that, as shown in Section 2.2, a proton, H^+, does not exist as such in aqueous solution. Instead it immediately combines with a water molecule to form the hydronium ion, H_3O^+.

Pattern 2: Take a proton away. If we run the "add a proton" reaction in reverse, then it corresponds to "take a proton away" from the ammonium ion and transfer it to the acetate ion. We can also use curved arrows to show the flow of electron pairs in this type of reaction as

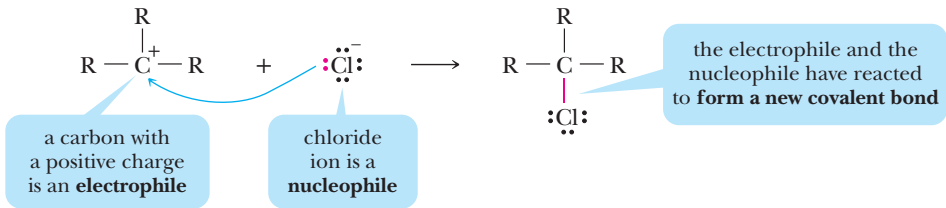
well. The mechanism for taking a proton away is similar to adding a proton, only we focus our attention on the compound that loses the proton.



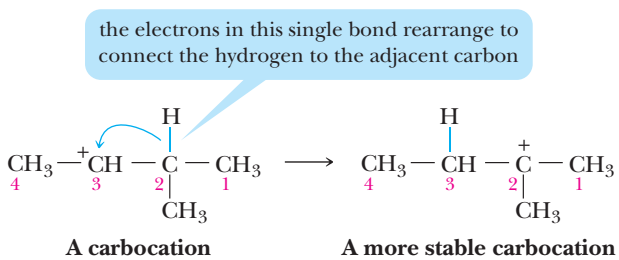
Pattern 3: Reaction of an electrophile and a nucleophile to form a new covalent bond. Another characteristic pattern is the reaction between an **electrophile** (an electron-poor species that can accept a pair of electrons to form a new covalent bond) and a **nucleophile** (an electron-rich species that can donate a pair of electrons to form a new covalent bond). An example of this type of reaction is that between a carbocation and halide ion. The driving force behind this reaction is the strong attraction between the positive and negative charges of the reacting species and the energy released when the new covalent bond forms. The following equation shows the flow of electron pairs in this type of reaction.

Electrophile An electron-poor species that can accept a pair of electrons to form a new covalent bond; alternatively, a Lewis acid (Section 2.6).

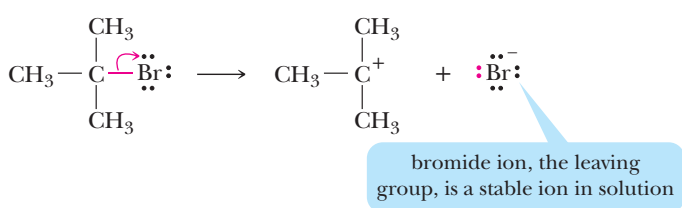
Nucleophile An electron-rich species that can donate a pair of electrons to form a new covalent bond; alternatively, a Lewis base (Section 2.6).



Pattern 4: Rearrangement of a bond. A common reaction that occurs in carbocations is the shift of a hydrogen or an alkyl group to place the positive charge at a more stable position. A rearrangement occurs when the electrons in a sigma bond break their bond from one carbon atom to form a new bond to another carbon atom as shown. The driving force for this process is the greater stability of the newly formed carbocation over the original. We will have more to say about rearrangements in Section 5.4.



Pattern 5: Break a bond to form a stable ion or molecule. A carbocation can also be formed when a chemical species breaks off from a molecule, taking the electrons from the former single bond with it. The chemical species that broke off is called a leaving group, and the bond breaks because it forms one or more stable ions or molecules. We will have more to say about leaving groups in Section 7.5C.



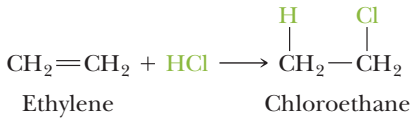
5.3 What Are the Mechanisms of Electrophilic Additions to Alkenes?

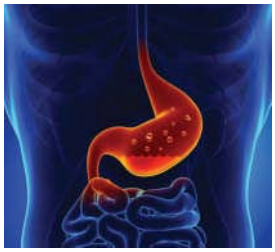
We begin our introduction to the chemistry of alkenes with an examination of three types of addition reactions: the addition of hydrogen halides (HCl, HBr, and HI), water (H_2O), and halogens (Cl_2, Br_2). We first study some of the experimental observations about each addition reaction and then its mechanism. By examining these particular reactions, we develop a general understanding of how alkenes undergo addition reactions.

As we will show for the addition reactions of alkenes and for the reactions of many other classes of organic compounds, high-electron-density regions of molecules or ions react with low-electron-density regions of other molecules or ions, often resulting in the formation of a new covalent bond. We call an electron-rich species a **nucleophile** (nucleus loving), meaning that it seeks a region of low electron density. We call a low-electron-density species an **electrophile** (electron loving), meaning that it seeks a region of high electron density. Note that nucleophiles are Lewis bases and electrophiles are Lewis acids (Section 2.6).

A. Addition of Hydrogen Halides

The hydrogen halides HCl, HBr, and HI add to alkenes to give haloalkanes (alkyl halides). These additions may be carried out either with the pure reagents or in the presence of a polar solvent such as acetic acid. The addition of HCl to ethylene gives chloroethane (ethyl chloride):

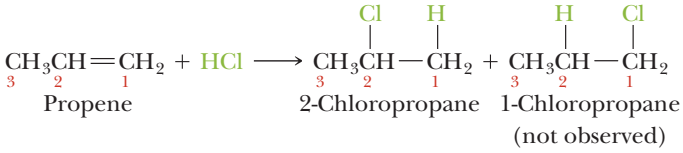




decade3d – anatomy online/ Shutterstock

The hydrochloric acid used in alkene reactions is the same acid found in gastric acid: $[HCl]_{gastric} = 0.1M$

The addition of HCl to propene gives 2-chloropropane (isopropyl chloride); hydrogen adds to carbon 1 of propene and chlorine adds to carbon 2. If the orientation of addition were reversed, 1-chloropropane (propyl chloride) would be formed. The observed result is that 2-chloropropane is formed to the virtual exclusion of 1-chloropropane:



Regioselective reaction A reaction in which one direction of bond forming or bond breaking occurs in preference to all other directions.

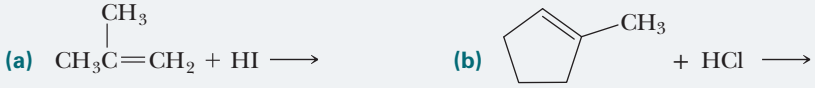
We say that the addition of HCl to propene is highly regioselective and that 2-chloropropane is the major product of the reaction. A **regioselective reaction** is a reaction in which one direction of bond forming or breaking occurs in preference to all other directions.

Markovnikov's rule In the addition of HX or H_2O to an alkene, hydrogen adds to the carbon of the double bond having the greater number of hydrogens.

Vladimir Markovnikov observed this regioselectivity and made the generalization, known as **Markovnikov's rule**, that, in the addition of HX to an alkene, hydrogen adds to the doubly bonded carbon that has the greater number of hydrogens already bonded to it. Although Markovnikov's rule provides a way to predict the product of many alkene addition reactions, it does not explain *why* one product predominates over other possible products.

EXAMPLE 5.2

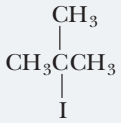
Name and draw a structural formula for the major product of each alkene addition reaction:



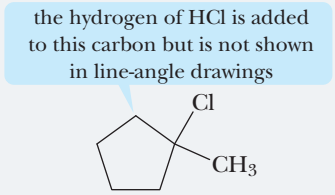
STRATEGY

Use Markovnikov's rule, which predicts that H adds to the least substituted carbon of the double bond and halogen adds to the more substituted carbon.

SOLUTION

(a) 

2-Iodo-2-methylpropane

(b) 

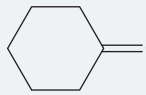
1-Chloro-1-methylcyclopentane

See problems 5.17–5.20, 5.28

PROBLEM 5.2

Name and draw a structural formula for the major product of each alkene addition reaction:

(a) $CH_3CH{=}CH_2 + HI \longrightarrow$

(b)  $+ HI \longrightarrow$

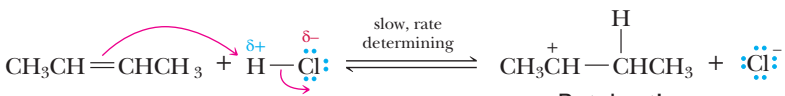
Chemists account for the addition of HX to an alkene by a two-step mechanism, which we illustrate in the following reaction of 2-butene with hydrogen chloride to give 2-chlorobutane. Let us first look at this two-step mechanism in general and then go back

Mechanism

Electrophilic Addition of HCl to 2-Butene

STEP 1: *Add a proton.*

The reaction begins with the transfer of a proton from HCl to 2-butene, as shown by the two curved arrows on the left side of Step 1:



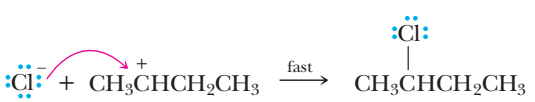
(a nucleophile) (an electrophile)

sec-Butyl cation (a 2°carbocation intermediate)

The first curved arrow shows the breaking of the pi bond of the alkene and its electron pair now forming a new covalent bond with the hydrogen atom of HCl. In this step, the carbon–carbon double bond of the alkene is the nucleophile (the electron-rich, nucleus-seeking species) and HCl is the electrophile (the electron-poor, electron-seeking species). The second curved arrow shows the breaking of the polar covalent bond in HCl and this electron pair being given entirely to chlorine, forming chloride ion. Step 1 in this mechanism results in the formation of an organic cation and chloride ion.

STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*

The reaction of the *sec*-butyl cation (an electrophile and a Lewis acid) with chloride ion (a nucleophile and a Lewis base) completes the valence shell of carbon and gives 2-chlorobutane:



Chloride ion (a Lewis base) (a nucleophile)

sec-Butyl cation (a Lewis acid) (an electrophile)

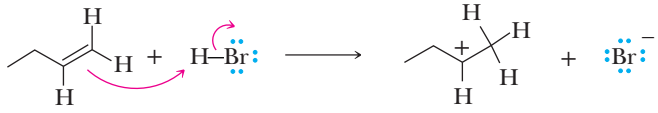
2-Chlorobutane

Draw Mechanisms

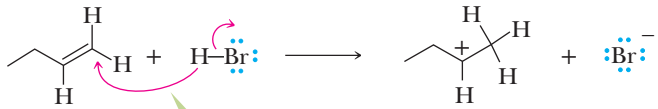
HOW TO 5.1

Mechanisms show how bonds are broken and formed. Although individual atoms may change positions in a reaction, the curved arrows used in a mechanism are only for the purpose of showing electron movement. Therefore, it is important to remember that curved arrow notation always shows the arrow originating from a bond or from an unshared electron pair (not the other way around).

Correct use of curved arrows...



Incorrect use of curved arrows...



and study each step in detail. There is a great deal of important organic chemistry embedded in these two steps, and it is crucial that you understand it now.

Step 1 results in the formation of an organic cation. One carbon atom in this cation has only six electrons in its valence shell and carries a charge of +1. A species containing a positively charged carbon atom is called a **carbocation** (*carbon* + *cation*). Carbocations are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbon atoms bonded directly to the carbon bearing the positive charge. All carbocations are Lewis acids (Section 2.6) and electrophiles.

Carbocation A species containing a carbon atom with only three bonds to it and bearing a positive charge.

In a carbocation, the carbon bearing the positive charge is bonded to three other atoms, and, as predicted by valence-shell electron-pair repulsion (VSEPR), the three bonds about that carbon are coplanar and form bond angles of approximately 120°. According to the orbital overlap model of bonding, the electron-deficient carbon of a carbocation uses its sp^2 hybrid orbitals to form sigma bonds to three groups. The unhybridized *2p* orbital lies perpendicular to the sigma bond framework and contains no electrons. A Lewis structure and an orbital overlap diagram for the *tert*-butyl cation are shown in Figure 5.3.

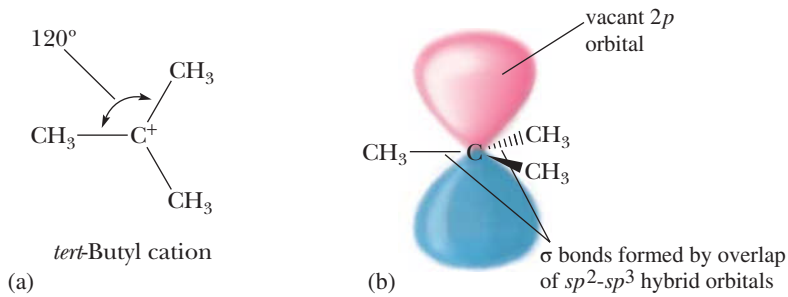


FIGURE 5.3 The structure of the *tert*-butyl cation. (a) Lewis structure and (b) an orbital picture.

Figure 5.4 shows an energy diagram for the two-step reaction of 2-butene with HCl. The slower, rate-determining step (the one that crosses the higher energy barrier) is Step 1, which leads to the formation of the 2° carbocation intermediate. This intermediate lies in an energy minimum between the transition states for Steps 1 and 2. As soon as the carbocation intermediate (a Lewis acid) forms, it reacts with chloride ion (a Lewis base) in a Lewis acid–base reaction to give 2-chlorobutane. Note that the energy level for 2-chlorobutane (the product) is lower than the energy level for 2-butene and HCl (the reactants). Thus, in this alkene addition reaction, heat is released; the reaction is, accordingly, exothermic.

Relative Stabilities of Carbocations: Regioselectivity and Markovnikov's Rule

The reaction of HX and an alkene can, at least in principle, give two different carbocation

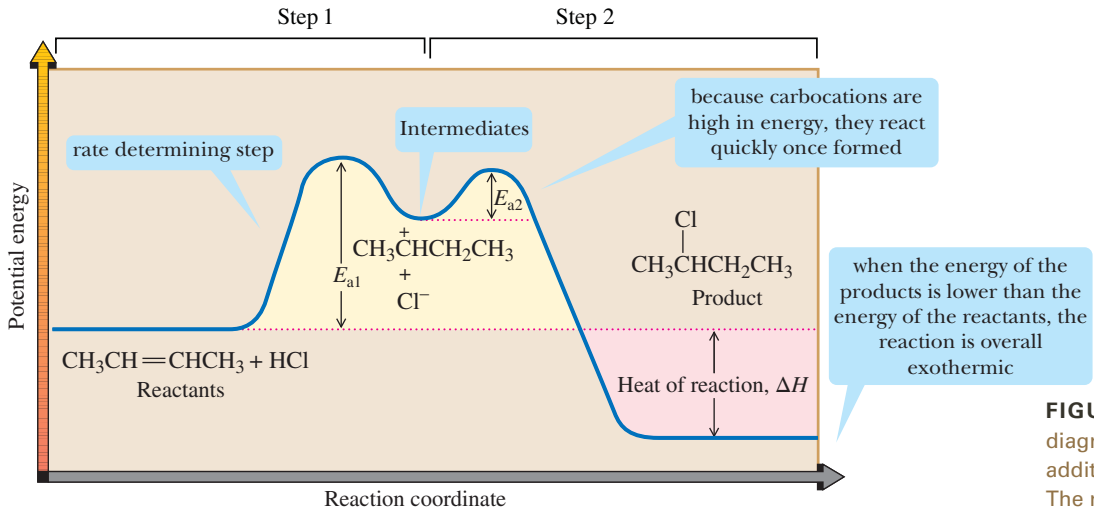
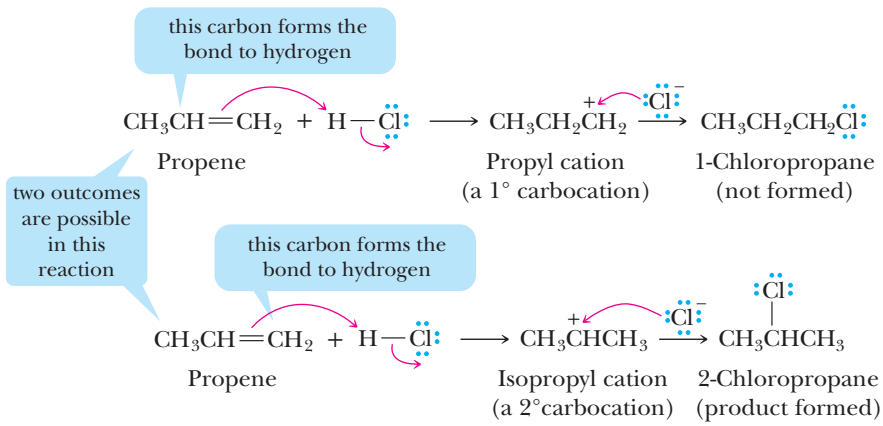


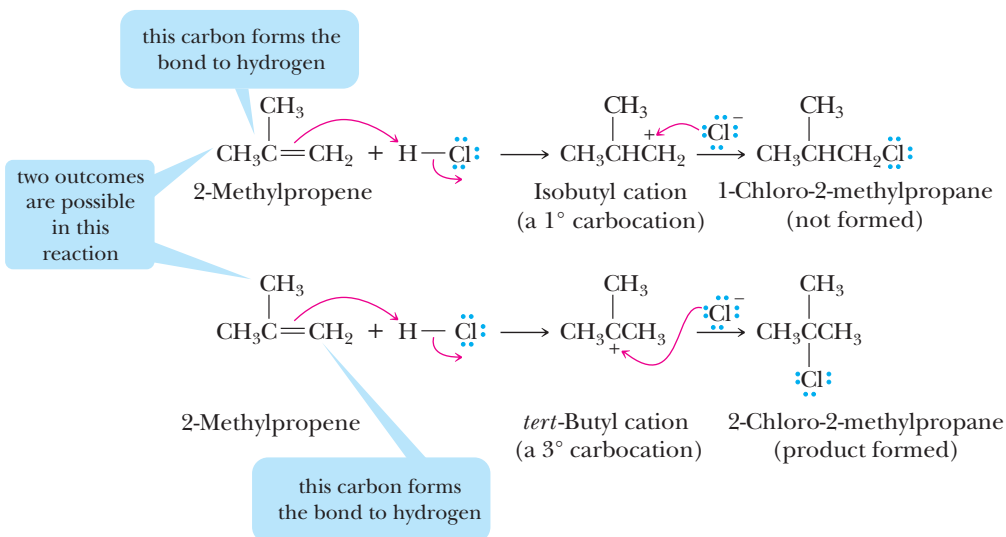
FIGURE 5.4 Energy diagram for the two-step addition of HCl to 2-butene. The reaction is exothermic.

intermediates, depending on which of the doubly bonded carbon atoms forms a bond with H^+, as illustrated by the reaction of HCl with propene:



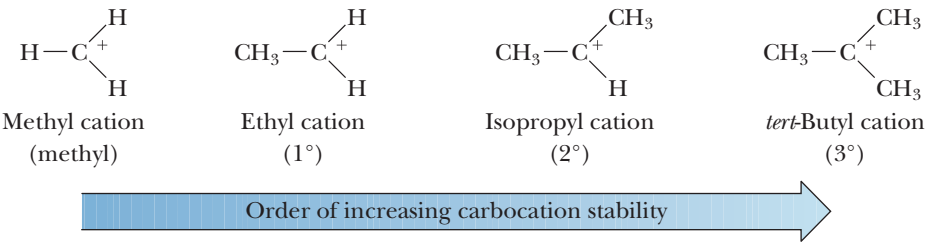
The observed product is 2-chloropropane. Because carbocations react very quickly with chloride ions, the absence of 1-chloropropane as a product tells us that the 2° carbocation is formed in preference to the 1° carbocation.

Similarly, in the reaction of HCl with 2-methylpropene, the transfer of a proton to the carbon–carbon double bond might form either the isobutyl cation (a 1° carbocation) or the *tert*-butyl cation (a 3° carbocation):



In this reaction, the observed product is 2-chloro-2-methylpropane, indicating that the 3° carbocation forms in preference to the 1° carbocation.

From such experiments and a great amount of other experimental evidence, we learn that a 3° carbocation is more stable and requires a lower activation energy for its formation than a 2° carbocation. A 2° carbocation, in turn, is more stable and requires a lower activation energy for its formation than a 1° carbocation. In fact, 1° carbocations are so unstable and so difficult to form that they are never observed in solution; they should never be proposed as a reaction intermediate when other more stable carbocations are an option. It follows that a more stable carbocation intermediate forms faster than a less stable carbocation intermediate. Following is the order of stability of four types of alkyl carbocations:



Although the concept of the relative stabilities of carbocations had not been developed in Markovnikov's time, their relative stabilities are the underlying basis for his rule; that is, the proton of H—X adds to the less substituted carbon of a double bond because this mode of addition produces the more stable carbocation intermediate.

Now that we know the order of stability of carbocations, how do we account for it? The principles of physics teach us that a system bearing a charge (either positive or negative) is more stable if the charge is delocalized. Using this principle, we can explain the order of stability of carbocations if we assume that alkyl groups bonded to a positively charged carbon release electrons toward the cationic carbon and thereby help delocalize the charge on the cation. The electron-releasing ability of alkyl groups bonded to a cationic carbon is accounted for by the **inductive effect** (Section 2.5C).

The inductive effect operates in the following way: The electron deficiency of the carbon atom bearing a positive charge exerts an electron-withdrawing inductive effect that polarizes electrons from adjacent sigma bonds toward it. Thus, the positive charge of the cation is not localized on the trivalent carbon, but rather is delocalized over nearby atoms as well. The larger the volume over which the positive charge is delocalized, the greater is the stability of the cation. Thus, as the number of alkyl groups bonded to the cationic carbon increases, the stability of the cation increases as well. Figure 5.5 illustrates the electron-withdrawing inductive effect of the positively charged carbon and the resulting delocalization of charge. According to quantum mechanical calculations, the charge on carbon in the methyl cation is approximately +0.645, and the charge on each of the hydrogen atoms is +0.118. Thus, even

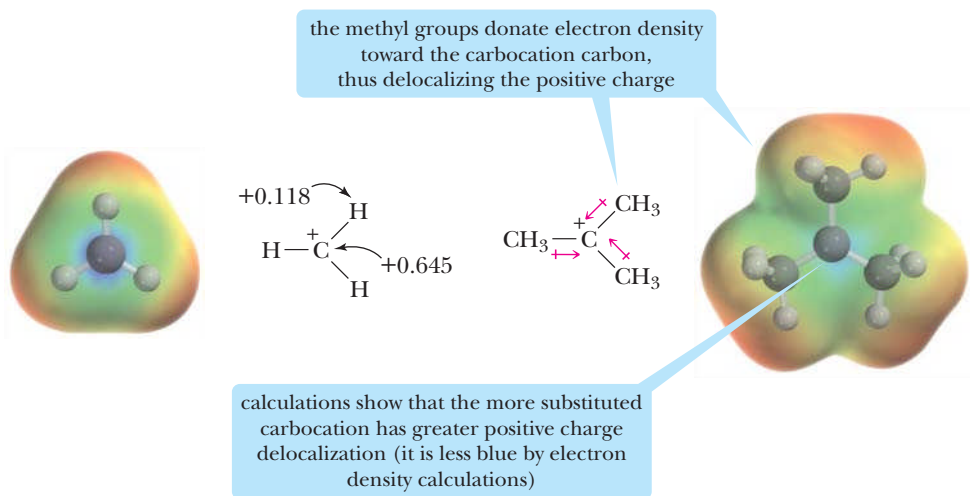
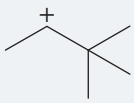
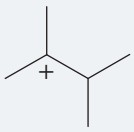
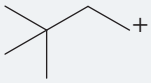


FIGURE 5.5 Methyl and *tert*-butyl cations. Delocalization of positive charge by the electron-withdrawing inductive effect of the trivalent, positively charged carbon according to molecular orbital calculations.

in the methyl cation, the positive charge is not localized on carbon. Rather, it is delocalized over the volume of space occupied by the entire ion. The polarization of electron density and the delocalization of charge are even more extensive in the *tert*-butyl cation.

EXAMPLE 5.3

Arrange these carbocations in order of increasing stability:

(a)  (b)  (c) 

STRATEGY

Determine the degree of substitution of the positively charged carbon and then consider the order of decreasing stability of alkyl carbocations is 3° > 2° > 1°.

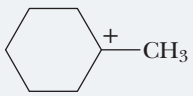
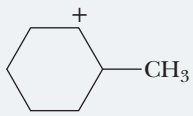
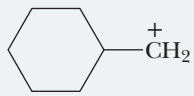
SOLUTION

See problems 5.15, 5.16

Carbocation (a) is secondary, (b) is tertiary, and (c) is primary. In order of increasing stability, they are $c < a < b$.

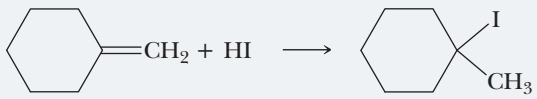
PROBLEM 5.3

Arrange these carbocations in order of increasing stability:

(a)  (b)  (c) 

EXAMPLE 5.4

Propose a mechanism for the addition of HI to methylenecyclohexane to give 1-iodo-1-methylcyclohexane:



Methylenecyclohexane 1-Iodo-1-methylcyclohexane

Which step in your mechanism is rate determining?

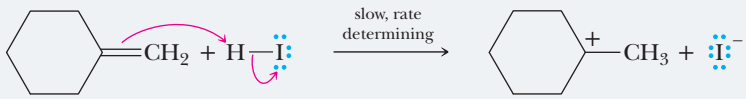
STRATEGY

Propose a two-step mechanism similar to that proposed for the addition of HCl to propene. Formation of the carbocation intermediate is rate determining.

SOLUTION

STEP 1: *Add a proton.*

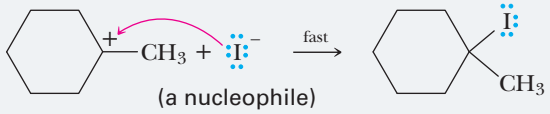
A rate-determining proton transfer from HI to the carbon–carbon double bond gives a 3° carbocation intermediate:



Methylenecyclohexane A 3° carbocation intermediate

STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*

Reaction of the 3° carbocation intermediate (a Lewis acid) with iodide ion (a Lewis base) completes the valence shell of carbon and gives the product:



(an electrophile) (a nucleophile) 1-Iodo-1-methylcyclohexane

See problem 5.29

PROBLEM 5.4

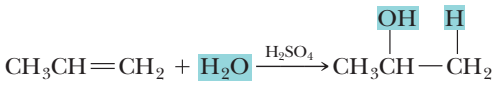
Propose a mechanism for the addition of HI to 1-methylcyclohexene to give 1-iodo-1-methylcyclohexane. Which step in your mechanism is rate determining?

B. Addition of Water: Acid-Catalyzed Hydration

Hydration Addition of water.

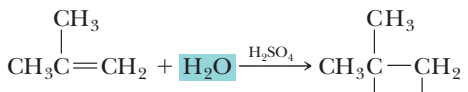
In the presence of an acid catalyst—most commonly, concentrated sulfuric acid—water adds to the carbon–carbon double bond of an alkene to give an alcohol. The addition of water is called **hydration**. In the case of simple alkenes, H adds to the carbon of the double bond with the greater number of hydrogens and OH adds to the carbon with the lesser number of hydrogens. Thus, H—OH adds to alkenes in accordance with Markovnikov's rule:

EXAMPLE 1



Propene 2-Propanol

EXAMPLE 2



2-Methylpropene 2-Methyl-2-propanol

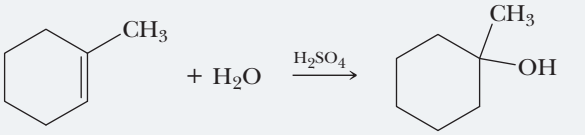
EXAMPLE 5.5

Draw a structural formula for the product of the acid-catalyzed hydration of 1-methylcyclohexene.

STRATEGY

Use Markovnikov's rule, which states that the H adds to the carbon of the carbon–carbon double bond bearing the greater number of hydrogens and that OH adds to the carbon bearing the lesser number of hydrogens.

SOLUTION

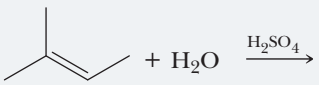


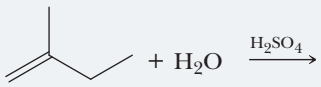
1-Methylcyclohexene 1-Methylcyclohexanol

See problems 5.19, 5.20, 5.28, 5.32

PROBLEM 5.5

Draw a structural formula for the product of each alkene hydration reaction:

(a) 

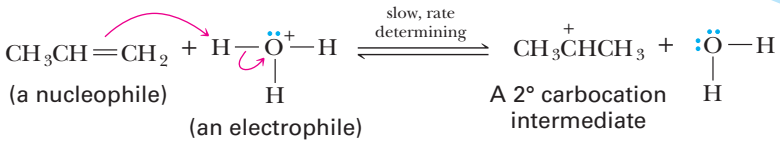
(b) 

The mechanism for the acid-catalyzed hydration of alkenes is quite similar to what we have already proposed for the addition of HCl, HBr, and HI to alkenes and is illustrated by the hydration of propene to 2-propanol. This mechanism is consistent with the fact that acid is a catalyst. An H_3O^+ is consumed in Step 1, but another is generated in Step 3.

Mechanism

Acid-Catalyzed Hydration of Propene

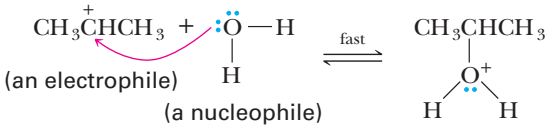
STEP 1: *Add a proton.*
Proton transfer from the acid catalyst, in this case, the hydronium ion, to propene gives a 2° carbocation intermediate (a Lewis acid):



hydronium ion is formed from the rapid transfer of a proton when the strong acid H_2SO_4 is added to water

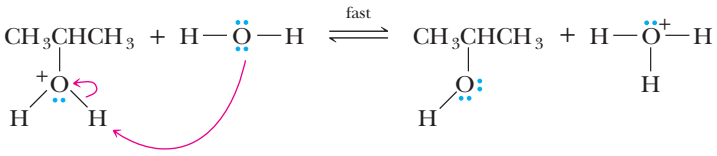
In this step, the carbon–carbon double bond of the alkene functions as a nucleophile and the hydronium ion functions as an electrophile.

STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction of the carbocation intermediate (a Lewis acid) with water (a Lewis base) completes the valence shell of carbon and gives an **oxonium ion**:



Oxonium ion An ion that contains an oxygen atom bonded to three other atoms or groups of atoms and bears a positive charge.

STEP 3: *Take a proton away.*
Proton transfer from the oxonium ion to water gives the alcohol and generates a new molecule of the catalyst:



EXAMPLE 5.6

Propose a mechanism for the acid-catalyzed hydration of methylenecyclohexane to give 1-methylcyclohexanol. Which step in your mechanism is rate determining?

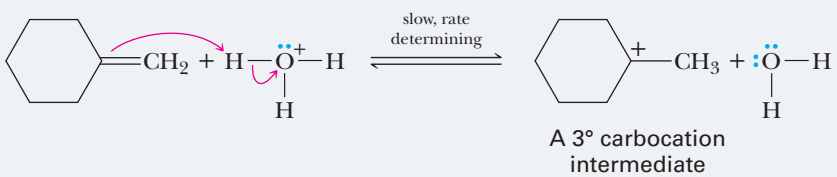
STRATEGY

Propose a three-step mechanism similar to that for the acid-catalyzed hydration of propene.

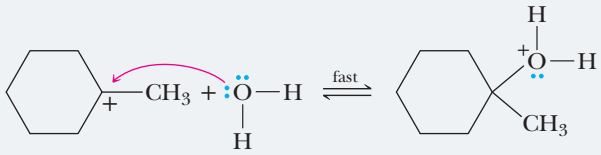
SOLUTION

The formation of the 3° carbocation intermediate in Step 1 is rate determining.

STEP 1: *Add a proton.*
Proton transfer from the acid catalyst to the alkene gives a 3° carbocation intermediate (a Lewis acid):

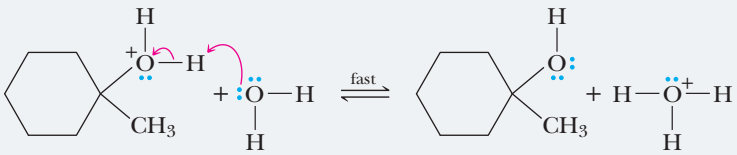


STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction of the carbocation intermediate (a Lewis acid) with water (a Lewis base) completes the valence shell of carbon and gives an oxonium ion:



An oxonium ion

STEP 3: *Take a proton away.*
Proton transfer from the oxonium ion to water gives the alcohol and regenerates the acid catalyst:



See problems 5.29–5.31, 5.38

PROBLEM 5.6

Propose a mechanism for the acid-catalyzed hydration of 1-methylcyclohexene to give 1-methylcyclohexanol. Which step in your mechanism is rate determining?

C. Addition of Bromine and Chlorine

Stereoselective reaction
A reaction in which one stereoisomer is formed or destroyed in preference to all others that might be formed or destroyed.

Anti stereoselectivity
Addition of atoms or groups of atoms from opposite sides or faces of a carbon–carbon double bond.

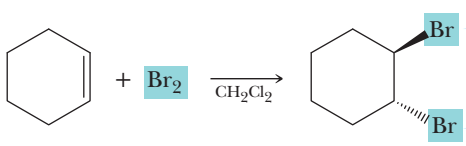
Chlorine (Cl_2) and bromine (Br_2) react with alkenes at room temperature by the addition of halogen atoms to the two carbon atoms of the double bond, forming two new carbon–halogen bonds:

$$CH_3CH{=}CHCH_3 + Br_2 \xrightarrow{CH_2Cl_2} CH_3\underset{\displaystyle Br}{\underset{|}{C}}H-\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

2-Butene — 2,3-Dibromobutane

Fluorine, F_2, also adds to alkenes, but because its reactions are very fast and difficult to control, addition of fluorine is not a useful laboratory reaction. Iodine, I_2, also adds, but the reaction is not preparatively useful.

The addition of bromine and chlorine to a cycloalkene gives a *trans* dihalocycloalkane. For example, the addition of bromine to cyclohexene gives *trans*-1,2-dibromocyclohexane; the *cis* isomer is not formed. Thus, the addition of a halogen to a cycloalkene is stereoselective. A **stereoselective reaction** is a reaction in which one stereoisomer is formed or destroyed in preference to all others that might be formed or destroyed. We say that addition of bromine to an alkene occurs with **anti stereoselectivity**.



Cyclohexene — *trans*-1,2-Dibromocyclohexane

In chemistry, a qualitative test is one in which evidence of a reaction is observable to the naked eye. The reaction of bromine with an alkene is a particularly useful qualitative test for the presence of a carbon–carbon double bond. If we dissolve bromine in dichloromethane, the solution turns red. Both alkenes and dibromoalkanes are colorless. If we now mix a few drops of the bromine solution with an alkene, a dibromoalkane is formed, and the solution becomes colorless.

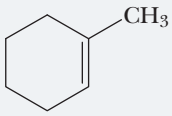
Charles D. Winters

A solution of bromine in dichloromethane is red. Add a few drops of an alkene and the red color disappears.

EXAMPLE 5.7

Complete these reactions, showing the stereochemistry of each product:

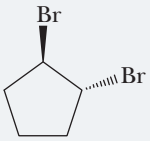
(a)  + Br_2 $\xrightarrow{CH_2Cl_2}$

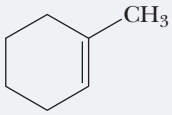
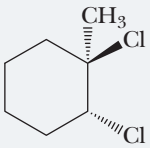
(b)  + Cl_2 $\xrightarrow{CH_2Cl_2}$

STRATEGY

The additions of both Br_2 and Cl_2 to cycloalkenes occurs with anti stereoselectivity; the two halogen atoms are *trans* to each other in the product.

SOLUTION

(a)  + Br_2 $\xrightarrow{CH_2Cl_2}$ 

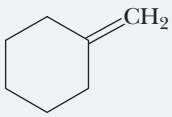
(b)  + Cl_2 $\xrightarrow{CH_2Cl_2}$ 

See problem 5.21

PROBLEM 5.7

Complete these reactions:

(a) $(CH_3)_3CCH{=}CH_2 + Br_2 \xrightarrow{CH_2Cl_2}$

(b)  + Cl_2 $\xrightarrow{CH_2Cl_2}$

Stereoselectivity and Bridged Halonium Ion Intermediates

We explain the addition of bromine and chlorine to cycloalkenes, as well as their anti stereoselectivity (they always add *trans* to each other), by a two-step mechanism that involves a halogen atom bearing a positive charge, called a **halonium ion**. The cyclic structure formed is called a **bridged halonium ion**. The bridged bromonium ion shown in the mechanism that follows might look odd to you, but it is an acceptable Lewis structure. A calculation of formal charge places a positive charge on bromine. Then, in Step 2, a bromide ion reacts with the bridged intermediate from the side opposite that occupied by the bromine atom, giving the dibromoalkane. Thus, bromine atoms add from opposite faces of the carbon–carbon double bond.

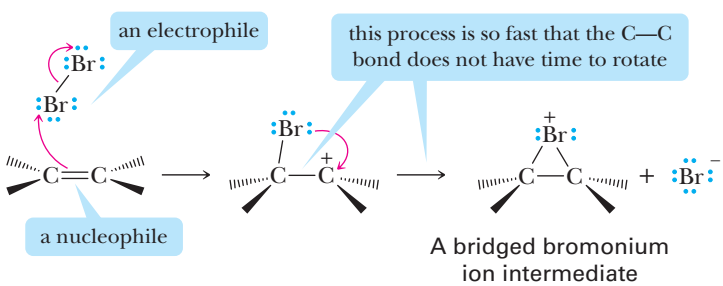
Halonium ion An ion in which a halogen atom bears a positive charge.

Mechanism

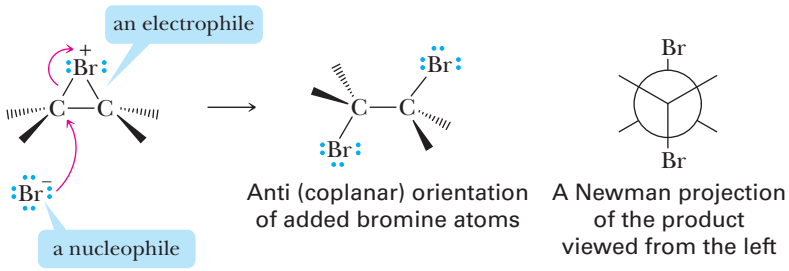
Addition of Bromine with Anti Selectivity

STEP 1: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*

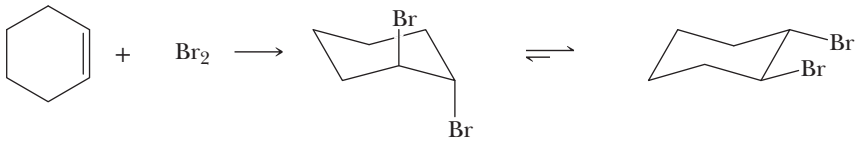
Reaction of the pi electrons of the carbon–carbon double bond (a nucleophile) with bromine (an electrophile) forms a bridged bromonium ion intermediate in which bromine bears a positive formal charge:



STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
A bromide ion (a nucleophile and a Lewis base) attacks carbon (an electrophile and a Lewis acid) from the side opposite the bridged bromonium ion, opening the three-membered ring:



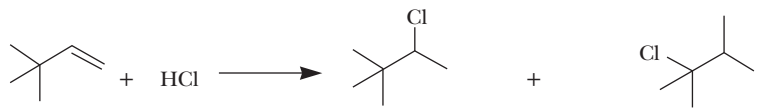
The addition of chlorine or bromine to cyclohexene and its derivatives gives a *trans* diaxial product because only axial positions on adjacent atoms of a cyclohexane ring are anti and coplanar. The initial *trans* diaxial conformation of the product is in equilibrium with the *trans* diequatorial conformation, and, in simple derivatives of cyclohexane, the latter is the more stable conformation and predominates.



5.4 What Are Carbocation Rearrangements?

Rearrangement A reaction in which a carbon group or hydrogen atom shifts its connectivity to another atom within the molecule.

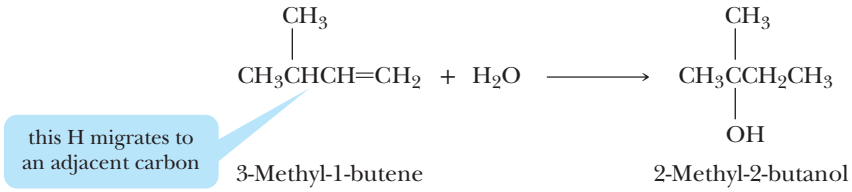
As we have seen in the preceding discussion, the expected product of electrophilic addition to a carbon–carbon double bond involves rupture of the π bond and formation of two new σ bonds in its place. In the addition of HCl to 3,3-dimethyl-1-butene, however, only 17% of 2-chloro-3,3-dimethylbutane, the expected product, is formed. The major product is 2-chloro-2,3-dimethylbutane, a compound with a different connectivity of its carbon atoms than that in the starting material. We say that the formation of 2-chloro-2,3-dimethylbutane involves a **rearrangement**. Typically, either an alkyl group or a hydrogen atom migrates, with its bonding pair of electrons, from an adjacent atom to an electron-deficient atom. In the rearrangements we examine in this chapter, migration is to an adjacent electron-deficient carbon atom bearing a positive charge. In other words, rearrangement is to the positively charged carbon of a carbocation.



Formation of the rearranged product in this reaction can be accounted for by the following mechanism, the key step of which is a type of rearrangement called a **1,2-shift**. In the rearrangement shown in Step 2, the migrating group is a methyl group with its pair of bonding electrons.

The driving force for this rearrangement is the fact that the less stable 2° carbocation is converted to a more stable 3° carbocation. From the study of this and other carbocation rearrangements, we find that 2° carbocations rearrange to 3° carbocations. 1° Carbocations are never observed for reactions taking place in solution and should not be proposed as reaction intermediates.

Rearrangements also occur in the acid-catalyzed hydration of alkenes, especially when a carbocation formed in the first step can rearrange to a more stable carbocation. For example, the acid-catalyzed hydration of 3-methyl-1-butene gives 2-methyl-2-butanol. In this example, the group that migrates is a hydrogen with its bonding pair of electrons, in effect, a hydride ion $H:^-$.

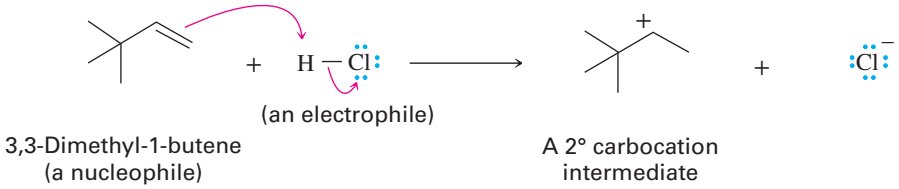


In summary, a rearrangement is likely to occur when a secondary carbocation forms and can rearrange by a 1,2-shift to a more stable tertiary carbocation.

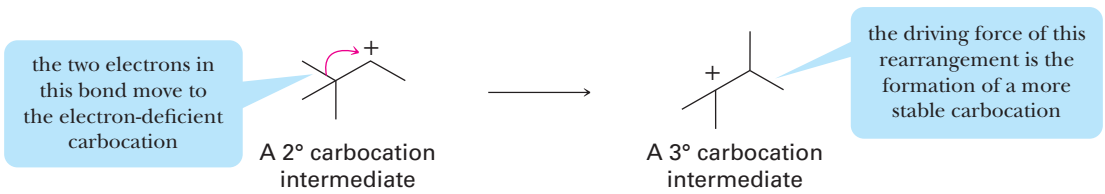
Mechanism

Rearrangement by a 1,2-Shift

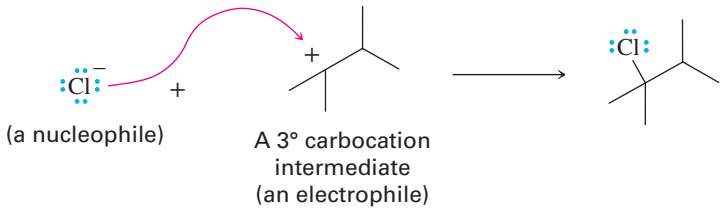
STEP 1: *Add a proton.*
Proton transfer from the HCl (an electrophile) to the alkene (a nucleophile) gives a 2° carbocation intermediate.



STEP 2: *Rearrangement of a bond.*
Migration of a methyl group with its bonding electrons from an adjacent carbon gives a more stable 3° carbocation intermediate. The major movement is that of the bonding electron pair with the methyl group following.



STEP 3: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction of the 3° carbocation intermediate (an electrophile and a Lewis acid) with chloride ion (a nucleophile and a Lewis base) gives the rearranged product.



EXAMPLE 5.8

Propose a mechanism for the acid-catalyzed hydration of 3-methyl-1-butene to give 2-methyl-2-butanol.

STRATEGY

Propose a mechanism similar to that proposed for the acid-catalyzed hydration of an alkene involving proton transfer from the acid catalyst to form a carbocation intermediate, rearrangement of the carbocation intermediate to a more stable intermediate, reaction of the more stable carbocation with water to form an oxonium ion, and finally proton transfer from the oxonium ion to water to

give the product and regenerate the acid catalyst. Lest you be tempted to use H^+ to initiate the reaction, remember that ionization of a strong acid in water generates a hydronium ion and an anion. Hydronium ion and not H^+ is the true catalyst in this reaction.

SOLUTION

STEP 1: *Add a proton.*

Proton transfer from the hydronium ion (the acid catalyst and electrophile) to the carbon–carbon double bond (the nucleophile) gives a 2° carbocation intermediate.

3-Methyl-1-butene (a nucleophile) | Hydronium ion (an electrophile) | A 2° carbocation intermediate

there is one hydrogen bonded to the carbocation carbon that is not drawn

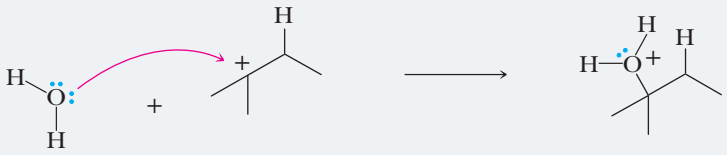
STEP 2: *Rearrangement of a bond.*

A 1,2-shift of a hydrogen from an adjacent carbon with its bonding pair of electrons to the positively charged carbon gives a more stable 3° carbocation intermediate.

A 2° carbocation intermediate | A 3° carbocation intermediate

STEP 3: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*

Reaction of the 3° carbocation (an electrophile and a Lewis acid) with a water molecule (a nucleophile and a Lewis base) completes the valence shell of carbon and gives an oxonium ion.



(a nucleophile) | A 3° carbocation intermediate (an electrophile) | An oxonium ion

STEP 4: *Take a proton away.*

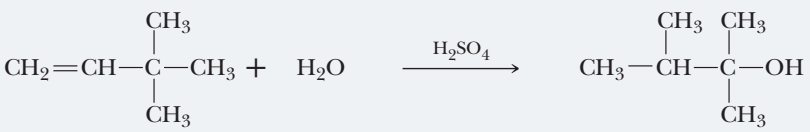
Proton transfer from the oxonium ion to water gives the alcohol and regenerates the acid catalyst.

An oxonium ion | Hydronium ion | 2-Methyl-2-butanol

See problems 5.29–5.31, 5.38

PROBLEM 5.8

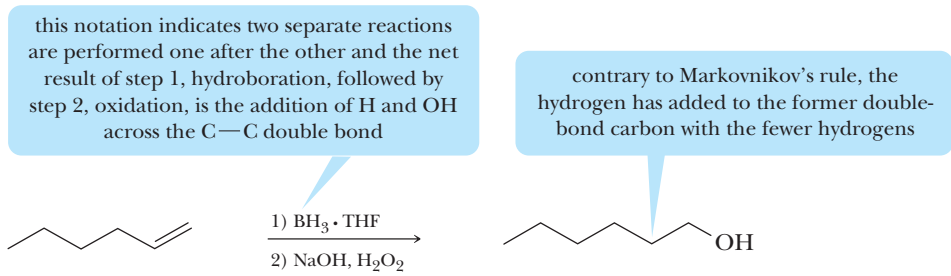
The acid-catalyzed hydration of 3,3-dimethyl-1-butene gives 2,3-dimethyl-2-butanol as the major product. Propose a mechanism for the formation of this alcohol.



3,3-Dimethyl-1-butene | 2,3-Dimethyl-2-butanol

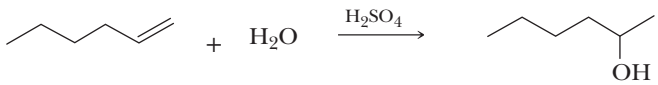
5.5 What Is Hydroboration–Oxidation of an Alkene?

The result of hydroboration and subsequent oxidation of an alkene is hydration of the carbon–carbon double bond, here illustrated by the hydroboration–oxidation of 1-hexene to give 1-hexanol.



Because hydrogen is added to the more substituted carbon of the double bond and —OH to the less substituted carbon, we refer to the regiochemistry of hydroboration and subsequent oxidation as **anti-Markovnikov hydration**.

Note by way of comparison that acid-catalyzed hydration of 1-hexene follows Markovnikov's rule and gives 2-hexanol.



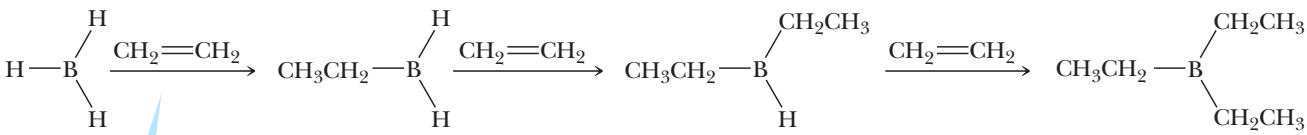
1-Hexene 2-Hexanol

The special value of hydration of an alkene by the combination of hydroboration–oxidation is that its regioselectivity is opposite that of acid-catalyzed hydration.

Hydroboration is the addition of borane, BH_3, to an alkene to form a trialkylborane. Borane cannot be prepared as a pure compound because it reacts with itself ($2BH_3 \rightarrow B_2H_6$) to form diborane B_2H_6, a toxic gas that ignites spontaneously in air. However, BH_3 forms a stable Lewis acid–base complex with ethers and is most commonly used as a commercially available solution of BH_3 in tetrahydrofuran (THF).

Tetrahydrofuran (THF) $BH_3 \cdot THF$

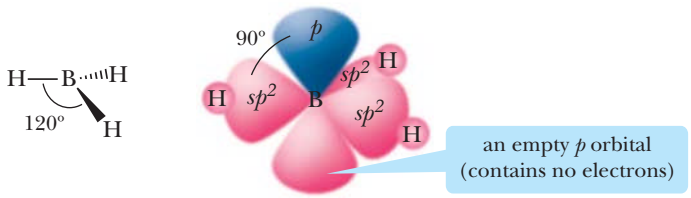
The overall reaction of BH_3 with a C—C double bond occurs in three steps. Borane reacts first with one molecule of the alkene to form an alkylborane, then with a second molecule of alkene to form a dialkylborane, and finally with a third molecule of alkene to form a trialkylborane. Although borane reacts with three equivalents of alkene to form the trialkylborane, we will focus on just the reaction of the first equivalent of C=C to explain the selectivities of the reaction.



we will focus on just this first reaction to explain the selectivities of the hydroboration reaction

Boron is a natural mineral that benefits bone and muscle growth and is sometimees taken as a supplement.

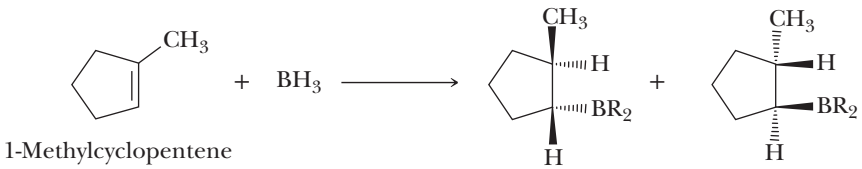
Boron, atomic number 5, has three electrons in its valence shell. To bond with three other atoms, boron uses sp^2 hybrid orbitals. Study the orbital model of BH_3 and take note of its types of orbitals and their geometrical arrangement. Because of the vacant $2p$ orbital in the valence shell of boron, BH_3, BF_3, and other tricovalent compounds of boron are electrophiles and closely resemble carbocations, except that they are electrically neutral.



Addition of borane to alkenes is regioselective and stereoselective in the following ways:

- Regioselective: In the addition of borane to an unsymmetrical alkene, boron becomes bonded predominantly to the less substituted carbon of the double bond.
- Stereoselective: Hydrogen and boron add from the same face of the double bond; that is, the reaction is **syn** (from the same side) **stereoselective**.

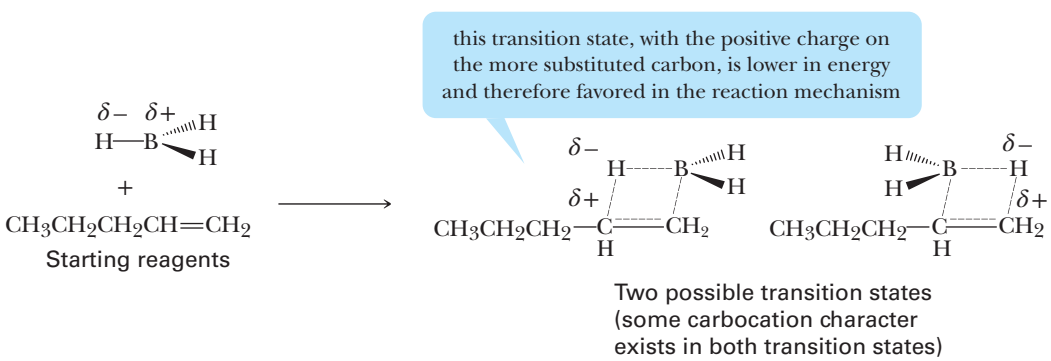
Both the regioselectivity and syn stereoselectivity are illustrated by hydroboration of 1-methylcyclopentene.



Mechanism

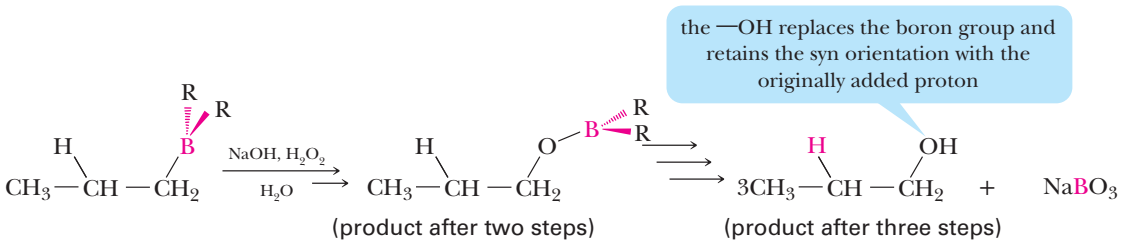
Hydroboration of an Alkene

STEP 1. *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
The addition of borane to an alkene is initiated by coordination of the vacant $2p$ orbital of boron (an electrophile) with the electron pair of the pi bond (a nucleophile). Chemists account for the stereoselectivity of hydroboration by proposing the formation of a cyclic, four-center transition state. Boron and hydrogen add simultaneously and from the same face of the double bond, with boron adding to the less substituted carbon atom of the double bond. This accounts for the syn stereoselectivity of the reaction. As shown in the mechanism, there is a slight polarity (about 5%) to the B—H bond because hydrogen (2.1) is slightly more electronegative than boron (2.0).



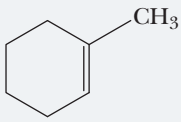
We account for the regioselectivity by steric factors. Boron, the larger part of the reagent, adds selectively to the less hindered carbon of the double bond, and hydrogen, the smaller part of the reagent, adds to the more hindered carbon. It is believed that the observed regioselectivity is due largely to steric effects.

STEP 2 AND BEYOND. Step 1 in this mechanism explains why the proton ends up on the less substituted carbon of the former C—C double bond and why the newly added boron and proton are added syn. While the mechanism of the next step, oxidation by hydrogen peroxide, is quite complicated and beyond the scope of this text, its function is to replace boron with —OH.



EXAMPLE 5.9

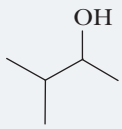
Draw structural formulas for the alcohol formed by hydroboration–oxidation of each alkene.

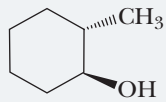
(a) $CH_3C(CH_3)=CHCH_3$ (b) 

STRATEGY

Hydroboration–oxidation is regioselective (—OH adds to the less substituted carbon of the carbon–carbon double bond, and —H adds to the more substituted carbon). It is also stereoselective (—H and —OH add to the same face of the double bond).

SOLUTION

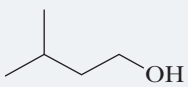
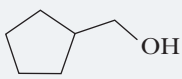
(a)  3-Methyl-2-butanol

(b)  *trans*-2-Methylcylohexanol

See problem 5.36

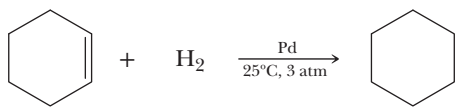
PROBLEM 5.9

Draw a structural formula for the alkene that gives each alcohol on hydroboration followed by oxidation.

(a)  (b) 

5.6 How Can an Alkene Be Reduced to an Alkane?

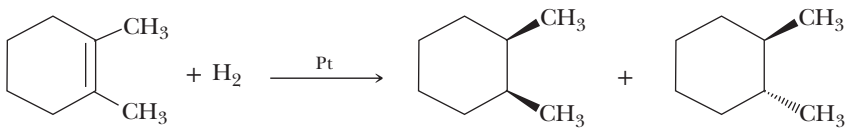
Most alkenes react quantitatively with molecular hydrogen, H_2, in the presence of a transition metal catalyst to give alkanes. Commonly used transition metal catalysts include platinum, palladium, ruthenium, and nickel. Yields are usually quantitative or nearly so. Because the conversion of an alkene to an alkane involves reduction by hydrogen in the presence of a catalyst, the process is called **catalytic reduction** or, alternatively, **catalytic hydrogenation**.



Cyclohexene Cyclohexane

The metal catalyst is used as a finely powdered solid, which may be supported on some inert material such as powdered charcoal or alumina. The reaction is carried out by dissolving the alkene in ethanol or another nonreacting organic solvent, adding the solid catalyst, and exposing the mixture to hydrogen gas at pressures from 1 to 100 atm. Alternatively, the metal may be chelated with certain organic molecules and used in the form of a soluble complex.

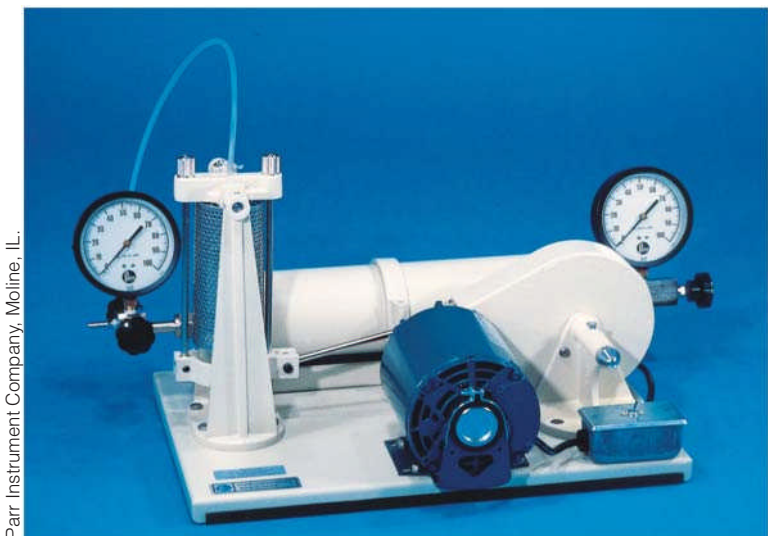
Catalytic reduction is stereoselective, the most common pattern being the **syn addition** of hydrogens to the carbon–carbon double bond. The catalytic reduction of 1,2-dimethylcyclohexene, for example, yields *cis*-1,2-dimethylcyclohexane along with lesser amounts of *trans*-1,2-dimethylcyclohexane.



1,2-Dimethylcyclohexene

70% to 85% *cis*-1,2-Dimethylcyclohexane

30% to 15% *trans*-1,2-Dimethylcyclohexane



Parr Instrument Company, Moline, IL.

A Parr shaker-type hydrogenation apparatus allows chemists to achieve gas pressures up to 100 atm.

The transition metals used in catalytic reduction are able to adsorb large quantities of hydrogen onto their surfaces, probably by forming metal–hydrogen sigma bonds. Similarly, these transition metals adsorb alkenes on their surfaces, with the formation of carbon–metal bonds [Figure 5.6(a)]. Hydrogen atoms are added to the alkene in two steps.

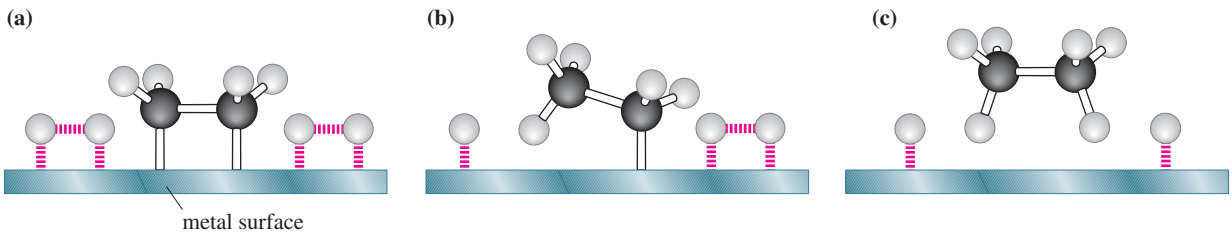


FIGURE 5.6 Syn addition of hydrogen to an alkene involving a transition metal catalyst. (a) Hydrogen and alkene are adsorbed on the metal surface, and (b) one hydrogen atom is transferred to the alkene, forming a new C—H bond. The other carbon remains adsorbed on the metal surface. (c) A second C—H bond forms, and the alkane is desorbed.

Heats of Hydrogenation and the Relative Stabilities of Alkenes

The **heat of hydrogenation** of an alkene is defined as its heat of reaction, $\Delta H°$, with hydrogen to form an alkane. Table 5.2 lists the heats of hydrogenation of several alkenes.

Three important points follow from the information given in Table 5.2.

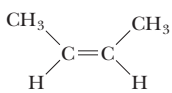
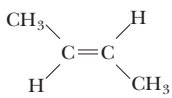
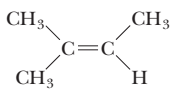
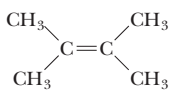
1. The reduction of an alkene to an alkane is an exothermic process. This observation is consistent with the fact that, during hydrogenation, there is net conversion of a weaker pi bond to a stronger sigma bond; that is, one sigma bond (H—H) and one pi bond (C═C) are broken, and two new sigma bonds (C—H) are formed.

2. The heat of hydrogenation depends on the degree of substitution of the carbon–carbon double bond: The greater the substitution, the lower is the heat of hydrogenation. Compare, for example, the heats of hydrogenation of ethylene (no substituents), propene (one substituent), 1-butene (one substituent), and the *cis* and *trans* isomers of 2-butene (two substituents each).

3. The heat of hydrogenation of a *trans*alkene is lower than that of the isomeric *cis*alkene. Compare, for example, the heats of hydrogenation of *cis*-2-butene and *trans*-2-butene. Because the reduction of each alkene gives butane, any difference in their heats of hydrogenation must be due to a difference in relative energy between the two alkenes (Figure 5.7). The alkene with the lower (less negative) value of $\Delta H°$ is the more stable alkene.

These features of a hydrogenation reaction allow us to compare the stabilities and reactivities of any two alkenes that would yield the same product upon hydrogenation. Thus we explain the greater stability of *trans* alkenes relative to *cis* alkenes in terms of nonbonded interaction strain. In *cis*-2-butene, the two $—CH_3$ groups are sufficiently close to each other that there is repulsion between their electron clouds. This repulsion is reflected in the larger heat of hydrogenation (decreased stability) of *cis*-2-butene compared with that of *trans*-2-butene (approximately 4.2 kJ/mol).

TABLE 5.2 Heats of Hydrogenation of Several Alkenes

Name	Structural Formula	ΔH [kJ (kcal/mol)]	
Ethylene	$CH_2═CH_2$	−137 (−32.8)	 Ethylene
Propene	$CH_3CH═CH_2$	−126 (−30.1)	
1-Butene	$CH_3CH_2CH═CH_2$	−127 (−30.3)	
cis-2-Butene		−120 (−28.6)	 *trans*-2-Butene
trans-2-Butene		−115 (−27.6)	
2-Methyl-2-butene		−113 (−26.9)	 2,3-Dimethyl-2-butene
2,3-Dimethyl-2-butene		−111 (−26.6)	

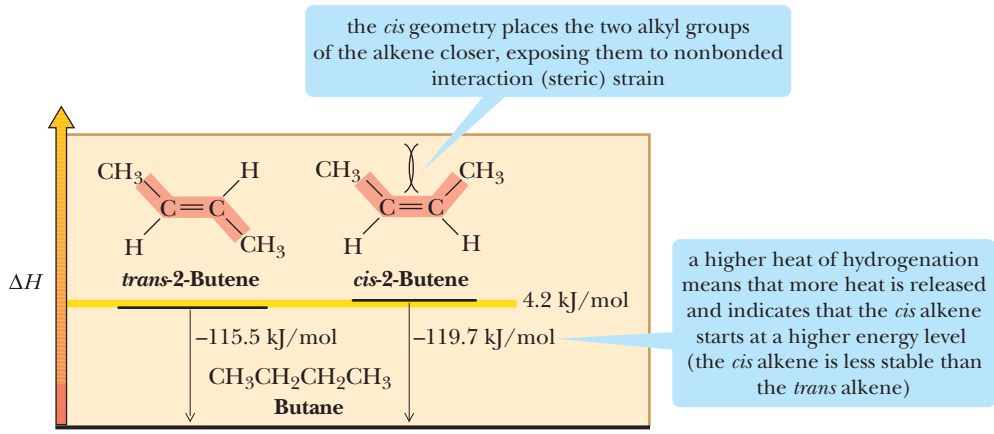
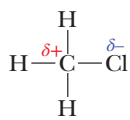


FIGURE 5.7 Heats of hydrogenation of *cis*-2-butene and *trans*-2-butene. *trans*-2-Butene is more stable than *cis*-2-butene by 4.2 kJ/mol (1.0 kcal/mol).

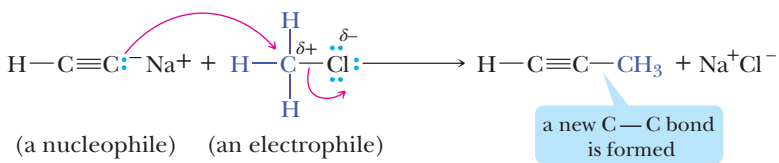
5.7 How Can an Acetylide Anion Be Used to Create a New Carbon–Carbon Bond?

In this section, we cover one of two very important reactions of alkynes for organic synthesis. As we have seen (Section 4.4) an acetylide anion is a strong base. It is also a nucleophile—it has an unshared pair of electrons that it can donate to an electrophilic carbon atom to form a new carbon–carbon bond.

To see how the use of an acetylide anion can lead to the formation of a new carbon–carbon bond, consider chloromethane, CH_3Cl. The C—Cl bond of chloromethane is polar covalent, with carbon bearing a partial positive charge because of the difference in electronegativity between carbon and chlorine.



In this instance, an acetylide anion donates its unshared pair of electrons to the carbon of chloromethane and in so doing displaces the halogen atom. Notice that this mechanism follows one of our common patterns, **the reaction of a nucleophile with an electrophile to form a new covalent bond**:



The important result is the formation of a new carbon–carbon bond. As is the case with so many organic reactions, this is an instance where reaction is brought about by the interaction of positive and negative charges of interacting molecules.

Because an alkyl group is added to the original alkyne molecule, this type of reaction is called an **alkylation reaction**. We limit our discussion in this chapter to reactions of acetylide anions with methyl and primary haloalkanes. We will discuss the scope and limitation of this type of nucleophilic substitution in more detail in Chapter 7. For reasons we will discuss there, alkylation of nucleophilic acetylide anions is practical only for methyl and primary halides. While this alkylation reaction can be used with limited success with secondary haloalkanes, it fails altogether for tertiary haloalkanes.

Because of the ready availability of acetylene and the ease with which it is converted to a nucleophile, alkylation of acetylide anions is the most convenient laboratory

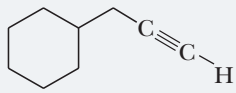
method used for the synthesis of other alkynes. The process can be repeated, and a terminal alkyne in turn can be converted to an internal alkyne. An important feature of this reaction is that a new carbon–carbon skeleton can be made, allowing for the construction of larger carbon skeletons from smaller ones. In the following scheme, the carbon skeleton of 3-heptyne is constructed from acetylene and two lower-molecular-weight haloalkanes.

$$HC{\equiv}CH \xrightarrow[2)\ CH_3CH_2Br]{1)\ NaNH_2} CH_3CH_2C{\equiv}CH \xrightarrow[4)\ CH_3CH_2CH_2Br]{3)\ NaNH_2} CH_3CH_2C{\equiv}CCH_2CH_2CH_3$$

Acetylene — 1-Butyne — 3-Heptyne

EXAMPLE 5.10

Propose a synthesis for each alkyne starting with acetylene and any necessary organic and inorganic reagents.

(a) 

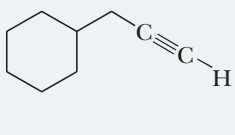
(b) $CH_3C{\equiv}CCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

(c) $CH_3C{\equiv}CCH_2CH_2CH_2CH_3$

STRATEGY

Each alkyne can be synthesized by alkylation of an appropriate alkyne anion. First decide which new carbon–carbon bond or bonds must be formed by alkylation and which alkyne anion nucleophile and haloalkane pair is required to give the desired product. Synthesis of a terminal alkyne from acetylene requires only one nucleophilic substitution, and synthesis of an internal alkyne from acetylene requires two nucleophilic substitutions.

SOLUTION

(a) $HC{\equiv}CH \xrightarrow[2)\ \text{Br}]{1)\ NaNH_2}$ 

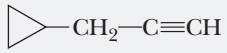
(b) $HC{\equiv}CH \xrightarrow[2)\ BrCH_3]{1)\ NaNH_2} CH_3C{\equiv}CH \xrightarrow[4)\ BrCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3]{3)\ NaNH_2} CH_3C{\equiv}CCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

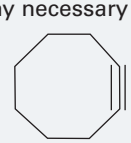
(c) $HC{\equiv}CH \xrightarrow[2)\ BrCH_3]{1)\ NaNH_2} CH_3C{\equiv}CH \xrightarrow[4)\ BrCH_2CH_2CH_2CH_3]{3)\ NaNH_2} CH_3C{\equiv}CCH_2CH_2CH_2CH_3$

See problem 5.50

PROBLEM 5.10

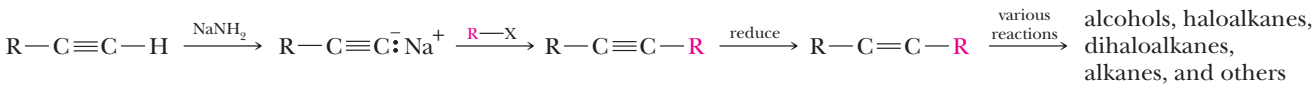
Propose a synthesis for each alkyne starting with acetylene and any necessary organic and inorganic reagents.

(a) 

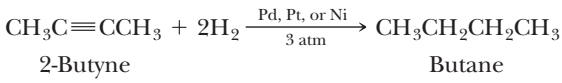
(b) 

5.8 How Can Alkynes Be Reduced to Alkenes and Alkanes?

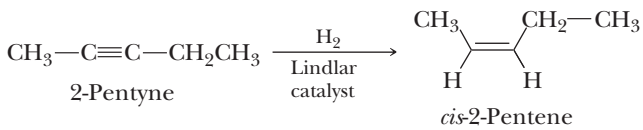
In the previous section, we saw how terminal alkynes can be used to form C—C bonds and synthesize larger alkynes. In this section, we will learn how alkynes can be reduced to alkanes and alkenes. Because of the rich number of reactions available to alkenes, we can now use these two reactions in tandem to synthesize a large variety of compounds:



Treatment of an alkyne with H_2 in the presence of a transition metal catalyst, most commonly Pd, Pt, or Ni, results in the addition of two moles of H_2 to the alkyne and its conversion to an alkane. Catalytic reduction of an alkyne can be brought about at or slightly above room temperature and with moderate pressures of hydrogen gas.



Reduction of an alkyne occurs in two stages: first, addition of one mole of H_2 to form an alkene and then addition of the second mole of H_2 to the alkene to form the alkane. In most cases, it is not possible to stop the reaction at the alkene stage. However, by careful choice of catalyst, it is possible to stop the reaction at the addition of one mole of hydrogen. The catalyst most commonly used for this purpose consists of finely powdered palladium metal deposited on solid calcium carbonate that has been specially modified with lead salts. This combination is known as the **Lindlar catalyst**. Reduction (hydrogenation) of alkynes over a Lindlar catalyst is stereoselective: **syn addition** of two hydrogen atoms to the carbon–carbon triple bond gives a *cis* alkene:



Because addition of hydrogen in the presence of the Lindlar catalyst is stereoselective for syn addition, it has been proposed that reduction proceeds by simultaneous or nearly simultaneous transfer of two hydrogen atoms from the surface of the metal catalyst to the alkyne. Earlier we presented a similar mechanism for the catalytic reduction of an alkene to an alkane (Section 5.6).

Organic chemistry is the foundation for the synthesis of new compounds such as medicines, agrochemicals, and plastics, to name just a few. In order to make these compounds, organic chemists must rely on a vast collection of reactions. The reactions presented in this chapter will already allow you to achieve the synthesis of complex molecules that may require multiple steps to make. As you continue your studies of organic chemistry, new reactions will be presented, the same reactions that have allowed for the creation of the millions of compounds that have contributed to the progress of civilization.

SUMMARY OF KEY QUESTIONS

5.1 What Are the Characteristic Reactions of Alkenes?

- A characteristic reaction of alkenes is **addition**, during which a pi bond is broken and sigma bonds are formed to two new atoms or groups of atoms. Alkene addition reactions include addition of halogen acids, H—Cl, acid-catalyzed addition of H_2O to form an alcohol, addition of halogens, X_2, hydroboration followed by oxidation to give an alcohol, and transition metal-catalyzed addition of H_2 to form an alkane.

5.2 What Is a Reaction Mechanism?

- A **reaction mechanism** is a description of (1) how and why a chemical reaction occurs, (2) which bonds break and which new ones form, (3) the order and relative rates in which the various bond-breaking and bond-forming steps take place, and (4) the role of the catalyst if the reaction involves a catalyst.
- **Transition state theory** provides a model for understanding the relationships among reaction rates, molecular structure, and energetics.
- A key postulate of transition state theory is that a **transition state** is formed in all reactions.
- The difference in energy between reactants and the transition state is called the **activation energy**.
- An **intermediate** is an energy minimum between two transition states.
- The slowest step in a multistep reaction, called the **rate-determining step**, is the one that crosses the highest energy barrier.
- There are many patterns that occur frequently in organic reaction mechanisms. These include **adding a proton, taking a proton away**, the **reaction of a nucleophile and electrophile to form a new bond**, and **rearrangement of a bond**.

5.3 What Are the Mechanisms of Electrophilic Additions to Alkenes?

- An **electrophile** is any molecule or ion that can accept a pair of electrons to form a new covalent bond. All electrophiles are Lewis acids.
- A **nucleophile** is an electron-rich species that can donate a pair of electrons to form a new covalent bond. All nucleophiles are Lewis bases.
- The rate-determining step in **electrophilic addition** to an alkene is reaction of an electrophile with a carbon–carbon double bond to form a **carbocation**, an ion that contains a carbon with only six electrons in its valence shell and has a positive charge.
- Carbocations are planar with bond angles of 120° about the positive carbon.
- The order of stability of carbocations is 3° > 2° > 1° > methyl. Primary carbocations, however, are so unstable and have such a high energy of activation for their formation that they are rarely formed in solution.
- **Electrophilic addition of a hydrogen halide** to an alkene is the addition of a halogen (Cl, Br, or I) and H across the carbon–carbon double bond. The reaction occurs with **Markovnikov regioselectivity** with the H adding to the carbon with the greater number of hydrogens.
- **Acid-catalyzed hydration** of an alkene is the addition of OH and H across the carbon–carbon double bond. The reaction occurs with Markovnikov regioselectivity.
- **Addition of bromine and chlorine** to an alkene is the addition of two halogens across the carbon–carbon double bond. The mechanism involves a **bridged halonium ion** as an intermediate and is an **anti stereoselective**.

5.4 What Are Carbocation Rearrangements?

- The driving force for a **carbocation rearrangement** is conversion of an initially formed carbocation to a more stable 2° or 3° carbocation.
- Rearrangement is by a **1,2-shift** in which an atom or group of atoms with its bonding electrons moves from an adjacent carbon to an electron-deficient carbon.

5.5 What Is Hydroboration–Oxidation of an Alkene?

- **Hydroboration** of an alkene is the addition of BH_2 and H across a C—C double bond.
- Hydroboration occurs with **anti-Markovnikov** regioselectivity with the H adding to the carbon with the fewer number of hydrogens.
- **Oxidation** of the hydroboration product results in the replacement of the boron group with an —OH group.
- **Hydroboration–oxidation** is **syn stereoselective**.

5.6 How Can an Alkene Be Reduced to an Alkane?

- The reaction of an alkene with H_2 in the presence of a transition metal catalyst converts all C—C double bonds in the alkene to C—C single bonds via the syn stereoselective addition of a hydrogen to each carbon of the former double bond.

- The **heats of reaction**, ΔH, of **hydrogenation reactions** can be used to compare the relative stabilities of alkenes.

5.7 How Can an Acetylide Anion Be Used to Create a New Carbon–Carbon Bond?

- **Acetylide anions** are both strong bases and nucleophiles. As nucleophiles, they can be alkylated by treatment with a methyl, primary, or secondary haloalkane. In this way, acetylene serves as a two-carbon building block for the synthesis of larger carbon skeletons.

5.8 How Can Alkynes Be Reduced to Alkenes and Alkanes?

- Treatment of alkyne with H_2 in the presence of a transition metal catalyst, most commonly Pd, Pt, or Ni, results in the addition of two moles of H_2 to the alkyne and its conversion to an alkane.
- Reduction of an alkyne using the **Lindlar catalyst** results in syn-stereoselective addition of one mole of H_2 to an alkyne. With this reagent, a disubstituted alkyne can be reduced to a *cis*-alkene.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Catalytic reduction of an alkene is syn stereoselective. (5.6)
2. Borane, BH_3, is a Lewis acid. (5.5)
3. All electrophiles are positively charged. (5.3)
4. Catalytic hydrogenation of cyclohexene gives hexane. (5.6)
5. A rearrangement will occur in the reaction of 2-methyl-2-pentene with HBr. (5.4)
6. All nucleophiles are negatively charged. (5.3)
7. In hydroboration, BH_3 behaves as an electrophile. (5.5)
8. In catalytic hydrogenation of an alkene, the reducing agent is the transition metal catalyst. (5.6)
9. Alkene addition reactions involve breaking a pi bond and forming two new sigma bonds in its place. (5.3)
10. The foundation for Markovnikov's rule is the relative stability of carbocation intermediates. (5.3)
11. Acid-catalyzed hydration of an alkene is regioselective. (5.3)
12. The mechanism for addition of HBr to an alkene involves one transition state and two reactive intermediates. (5.3)
13. Hydroboration of an alkene is regioselective and stereoselective. (5.5)
14. According to the mechanism given in the text for acid-catalyzed hydration of an alkene, the —H and —OH groups added to the double bond both arise from the same molecule of H_2O. (5.3)
15. Acid-catalyzed addition of H_2O to an alkene is called *hydration*. (5.3)
16. If a compound fails to react with Br_2, it is unlikely that the compound contains a carbon–carbon double bond. (5.3)
17. Addition of Br_2 and Cl_2 to cyclohexene is anti-stereoselective. (5.3)
18. A carbocation is a carbon that has four bonds to it and bears a positive charge. (5.3)
19. The geometry about the positively charged carbon of a carbocation is best described as trigonal planar. (5.3)
20. The carbocation derived by proton transfer to ethylene is CH_3CH_2+. (5.3)
21. Alkyl carbocations are stabilized by the electron-withdrawing inductive effect of the positively charged carbon of the carbocation. (5.3)
22. The oxygen atom of an oxonium ion obeys the octet rule. (5.3)
23. Markovnikov's rule refers to the regioselectivity of addition reactions to carbon–carbon double bonds. (5.3)
24. A rearrangement, in which a hydride ion shifts, will occur in the reaction of 3-methyl-1-pentene with HCl. (5.4)
25. Acid-catalyzed hydration of 1-butene gives 1-butanol, and acid-catalyzed hydration of 2-butene gives 2-butanol. (5.3)
26. Alkenes are good starting materials for reactions in which it is necessary to form a C—C bond. (5.7)
27. Alkynes can be reduced to *cis* alkenes. (5.8)

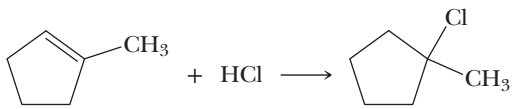
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1)T (2)T (3) F (4) F (5) F (6) F (7)T (8) F (9)T (10)T (11)T (12) F (13)T (14) F (15)T (16)T (17)T (18) F (19)T (20)T (21)T (22)T (23)T (24)T (25) F (26) F (27)T

KEY REACTIONS

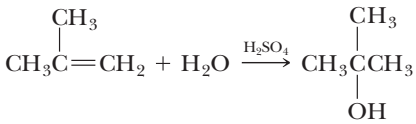
1. Addition of H—X to an Alkene (Section 5.3A)

The addition of H—X is regioselective and follows Markovnikov's rule. Reaction occurs in two steps and involves the formation of a carbocation intermediate:



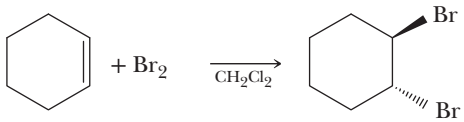
2. Acid-Catalyzed Hydration of an Alkene (Section 5.3B)

Hydration of an alkene is regioselective and follows Markovnikov's rule. Reaction occurs in two steps and involves the formation of a carbocation intermediate:



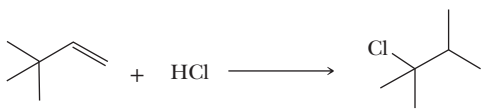
3. Addition of Bromine and Chlorine to an Alkene (Section 5.3C)

Addition of halogen occurs in two steps and involves anti-stereoselective addition by way of a bridged bromonium or chloronium ion intermediate:



4. Carbocation Rearrangements (Section 5.4)

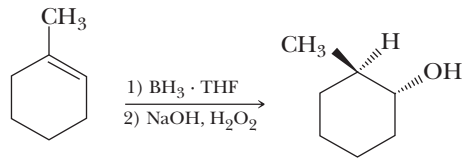
Rearrangement is from a less stable carbocation intermediate to a more stable one by a 1,2-shift. Rearrangements often occur during the hydrochlorination and acid-catalyzed hydration of alkenes.



3,3-Dimethyl-1-butene 2-Chloro-2,3-dimethylbutane

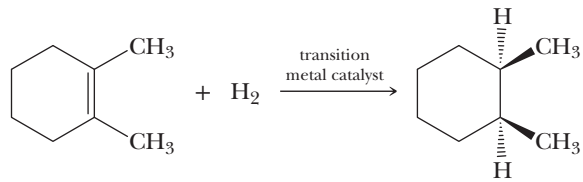
5. Hydroboration–Oxidation of an Alkene (Section 5.5)

Addition of BH_3 to an alkene is syn-stereoselective and regioselective: boron adds to the less substituted carbon of the double bond, and hydrogen adds to the more substituted carbon. Hydroboration–oxidation results in anti-Markovnikov hydration of the alkene.



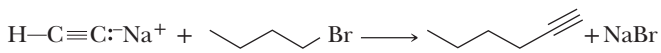
6. Reduction of an Alkene: Formation of Alkanes (Section 5.6)

Catalytic reduction involves predominantly the syn-stereoselective addition of hydrogen:



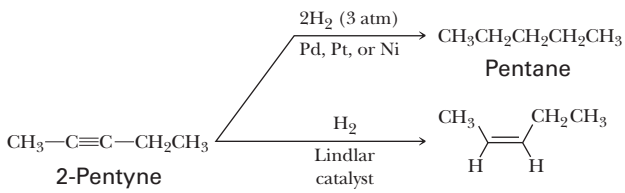
7. Alkylation on an Acetylide Anion (Section 5.7)

Acetylide anions are nucleophiles and displace halogen from methyl and 1° haloalkanes. Alkylation of acetylide anions is a valuable way to assemble a larger carbon skeleton.



8. Reduction of an Alkyne (Section 5.8)

Several different reagents reduce alkynes. Catalytic reduction using a transition metal catalyst gives an alkane. Catalytic reduction using a specially prepared catalyst called the Lindlar catalyst gives a *cis* alkene.



PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 5.2 Energy Diagrams

5.11 Describe the differences between a transition state and a reaction intermediate.

5.12 Sketch an energy diagram for a one-step reaction that is very slow and only slightly exothermic. How many transition states are present in this reaction? How many intermediates are present? **(See Example 5.1)**

5.13 Sketch an energy diagram for a two-step reaction that is endothermic in the first step, exothermic in the second step, and exothermic overall. How many transition states are present in this two-step reaction? How many intermediates are present? **(See Example 5.1)**

5.14 Determine whether each of the following statements is true or false, and provide a rationale for your decision:

(a) A transition state can never be lower in energy than the reactants from which it was formed.

(b) An endothermic reaction cannot have more than one intermediate.

(c) An exothermic reaction cannot have more than one intermediate.

(d) The rate-determining step is the step with the largest difference in energy between products and reactants.

(e) Transition states exist for long periods of time, but can be readily isolated.

SECTIONS 5.3–5.5 Electrophilic Additions to Alkenes, Rearrangements, and Hydroboration–Oxidation

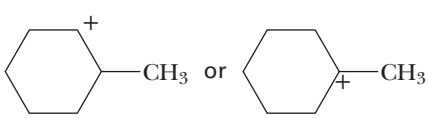
Study Suggestion. Instead of attempting all of these problems in one sitting, try half now and half at a later date. Breaking up your practice will result in more cumulative learning.

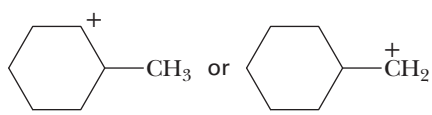
5.15 From each pair, select the more stable carbocation: **(See Example 5.3)**

(a) $CH_3CH_2CH_2^+$ or $CH_3\overset{+}{C}HCH_3$

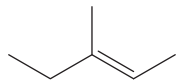
(b) $CH_3CH(CH_3)\overset{+}{C}HCH_3$ or $CH_3\overset{+}{C}(CH_3)CH_2CH_3$

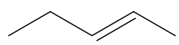
5.16 From each pair, select the more stable carbocation: **(See Example 5.3)**

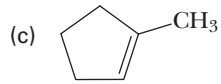
(a) 

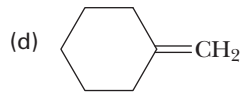
(b) 

5.17 Draw structural formulas for the isomeric carbocation intermediates formed by the reaction of each alkene with HCl. Label each carbocation as primary, secondary, or tertiary, and state which, if either, of the isomeric carbocations is formed more readily. **(See Example 5.2)**

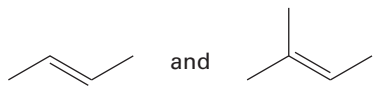
(a) 

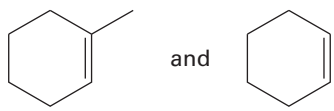
(b) 

(c) 

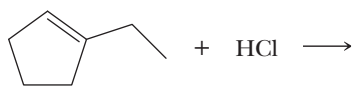
(d) 

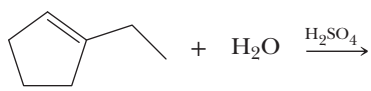
5.18 From each pair of compounds, select the one that reacts more rapidly with HI, draw the structural formula of the major product formed in each case, and explain the basis for your ranking: **(See Example 5.2)**

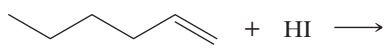
(a) 

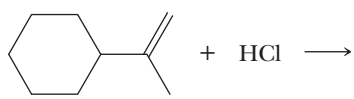
(b) 

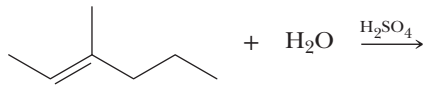
5.19 Complete these equations by predicting the major product formed in each reaction: **(See Examples 5.2, 5.5)**

(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

5.20 The reaction of 2-methyl-2-pentene with each reagent is regioselective. Draw a structural formula for the product of each reaction, and account for the observed regioselectivity. **(See Examples 5.2, 5.5, 5.9)**

(a) HI

(b) H_2O in the presence of H_2SO_4

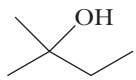
(c) BH_3 followed by H_2O_2, NaOH

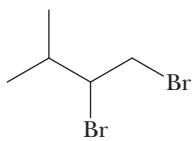
5.21 The addition of bromine and chlorine to cycloalkenes is stereoselective. Predict the stereochemistry of the product formed in each reaction: **(See Example 5.7)**

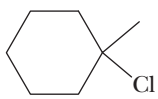
(a) 1-Methylcyclohexene + Br_2

(b) 1,2-Dimethylcyclopentene + Cl_2

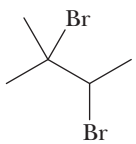
5.22 Draw a structural formula for an alkene with the indicated molecular formula that gives the compound shown as the major product. Note that more than one alkene may give the same compound as the major product.

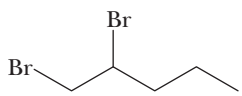
(a) $C_5H_{10} + H_2O \xrightarrow{H_2SO_4}$ 

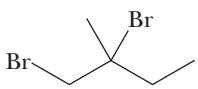
(b) $C_5H_{10} + Br_2 \longrightarrow$ 

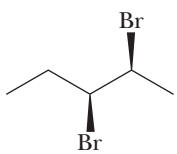
(c) $C_7H_{12} + HCl \longrightarrow$ 

5.23 Draw the structural formula for an alkene with the molecular formula C_5H_{10} that reacts with Br_2 to give each product:

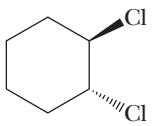
(a) 

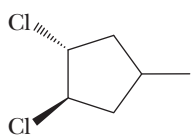
(b) 

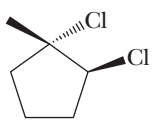
(c) 

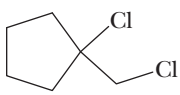
(d) 

5.24 Draw the structural formula for a cycloalkene with the molecular formula C_6H_{10} that reacts with Cl_2 to give each compound:

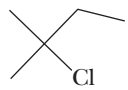
(a) 

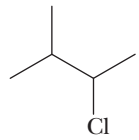
(b) 

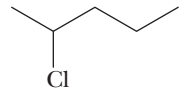
(c) 

(d) 

5.25 Draw the structural formula for an alkene with the molecular formula C_5H_{10} that reacts with HCl to give the indicated chloroalkane as the major product:

(a) 

(b) 

(c) 

5.26 Draw the structural formula of an alkene that undergoes acid-catalyzed hydration to give the indicated alcohol as the major product. More than one alkene may give each compound as the major product.

(a) 3-Hexanol

(b) 1-Methylcyclobutanol

(c) 2-Methyl-2-butanol

(d) 2-Propanol

5.27 Draw the structural formula of an alkene that undergoes acid-catalyzed hydration to give each alcohol as the major product. More than one alkene may give each compound as the major product.

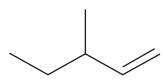
(a) Cyclohexanol

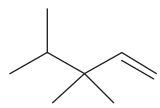
(b) 1,2-Dimethylcyclopentanol

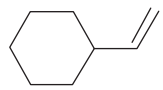
(c) 1-Methylcyclohexanol

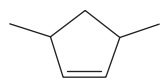
(d) 1-Isopropyl-4-methylcyclohexanol

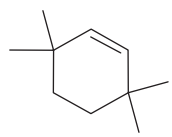
5.28 Complete these equations by predicting the major product formed in each reaction. Note that some of these reactions involve rearrangements. **(See Examples 5.2, 5.5)**

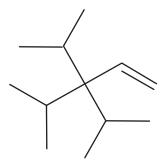
(a)  + HBr $\longrightarrow$

(b)  + $H_2O \xrightarrow{H_2SO_4}$

(c)  + $H_2O \xrightarrow{H_2SO_4}$

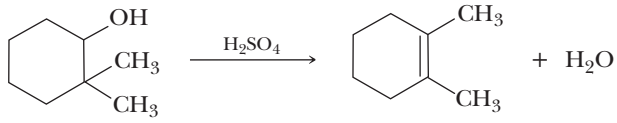
(d)  + HI $\longrightarrow$

(e)  + HCl $\longrightarrow$

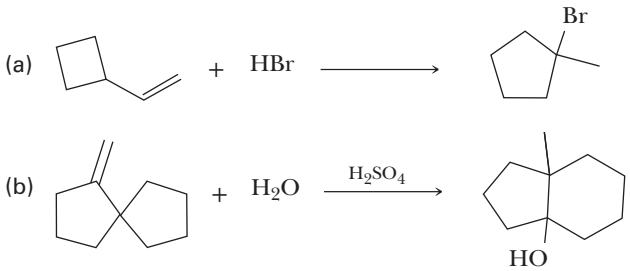
(f)  + $H_2O \xrightarrow{H_2SO_4}$

5.29 Propose a mechanism for each reaction in Problem 5.28. **(See Examples 5.4, 5.6, 5.8)**

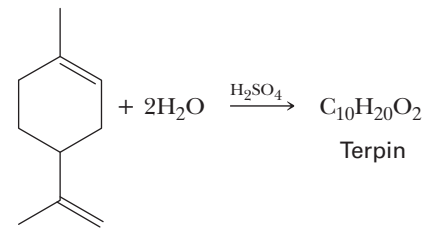
5.30 Propose a mechanism for the following acid-catalyzed dehydration. **(See Examples 5.6, 5.8)**



5.31 Propose a mechanism for each of the following transformations. **(See Examples 5.4, 5.6, 5.8)**



***5.32** Terpin is prepared commercially by the acid-catalyzed hydration of limonene: **(See Example 5.5)**



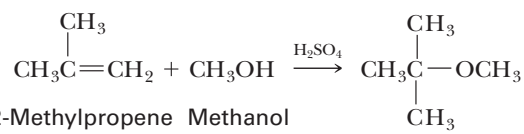
(a) Propose a structural formula for terpin and a mechanism for its formation.

(b) How many *cis–trans* isomers are possible for the structural formula you propose?

(c) Terpin hydrate, the isomer in terpin in which the one-carbon and three-carbon substituents are *cis* to each other, is used as an expectorant in cough medicines. Draw the alternative chair conformations for terpin hydrate, and state which of the two is the more stable.

5.33 Propose a mechanism for this reaction and account for its regioselectivity.

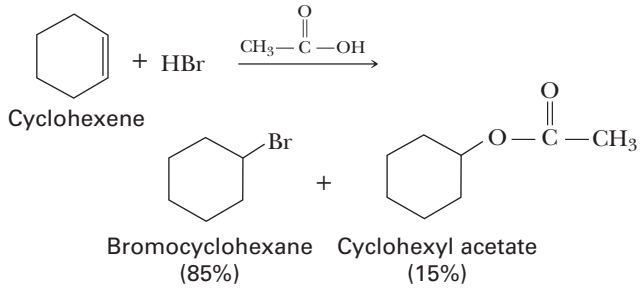
***5.34** The treatment of 2-methylpropene with methanol in the presence of a sulfuric acid catalyst gives *tert*-butyl methyl ether:



2-Methylpropene Methanol *tert*-Butyl methyl ether

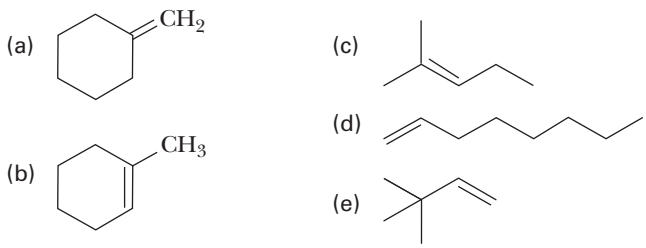
Propose a mechanism for the formation of this ether, which was used for many years as a gasoline additive until it was implicated as a contaminant in groundwater.

5.35 Treating cyclohexene with HBr in the presence of acetic acid gives a mixture of bromocyclohexane and cyclohexyl acetate.

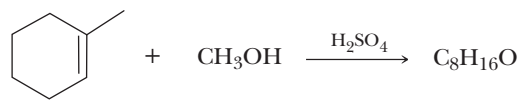


Account for the formation of each product but do not be concerned with the relative percentages of each.

5.36 Draw a structural formula for the alcohol formed by treating each alkene with borane in tetrahydrofuran (THF), followed by hydrogen peroxide in aqueous sodium hydroxide, and specify the stereochemistry where appropriate. **(See Example 5.9)**



5.37 Treatment of 1-methylcyclohexene with methanol in the presence of a sulfuric acid catalyst gives a compound with the molecular formula $C_8H_{16}O$. Propose a structural formula for this compound and a mechanism for its formation.



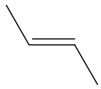
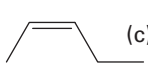
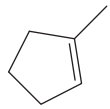
1-Methylcyclohexene Methanol

5.38 *cis*-3-Hexene and *trans*-3-hexene are different compounds and have different physical and chemical properties. Yet, when treated with H_2O/H_2SO_4, each gives the same alcohol. What is the alcohol, and how do you account for the fact that each alkene gives the same one? **(See Examples 5.6, 5.8)**

SECTION 5.6 Oxidation–Reduction

***5.39** Write a balanced equation for the combustion of 2-methylpropene in air to give carbon dioxide and water. The oxidizing agent is O_2, which makes up approximately 20% of air.

5.40 Draw the product formed by treating each alkene with H_2/Ni:

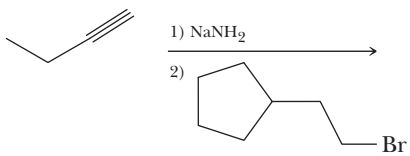
(a)  (b)  (c)  (d) 

5.41 Hydrocarbon A, C_5H_8, reacts with 2 moles of Br_2 to give 1,2,3,4-tetrabromo-2-methylbutane. What is the structure of hydrocarbon A?

5.42 Two alkenes, A and B, each have the formula C_5H_{10}. Both react with H_2/Pt and with HBr to give identical products. What are the structures of A and B?

SECTIONS 5.7—5.8 Reactions of Alkynes

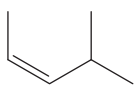
5.43 Complete these equations by predicting the major products formed in each reaction. If more than one product is equally likely, draw both products.

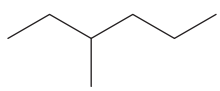
(a) 

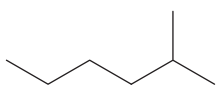
(b) 

(c) $(CH_3)_2CHCCH$ $\xrightarrow[2)\ CH_3(CH_2)_4Br\ \ 3)\ H_2/Pd\cdot C]{1)\ NaNH_2}$

5.44 Determine the alkyne that would be required in the following sequences of reactions.

(a) ? $\xrightarrow[2)\ CH_3CHBrCH_3\ \ 3)\ H_2/Lindlars]{1)\ NaNH_2}$ 

(b) ? $\xrightarrow[2)\ CH_3I\ \ 3)\ H_2/Ni]{1)\ NaNH_2}$ 

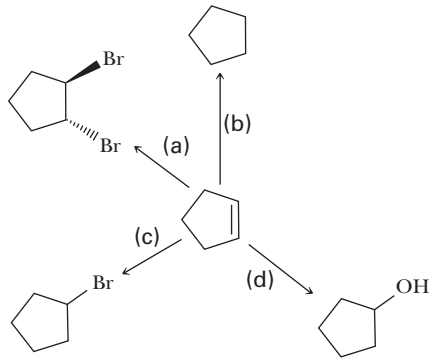
(c) ? $\xrightarrow[3)\ NaNH_2\ \ 4)\ (CH_3)_2CHCH_2Br\ \ 5)\ H_2/Pd\cdot C]{1)\ NaNH_2\ \ 2)\ CH_3I}$ 

Synthesis

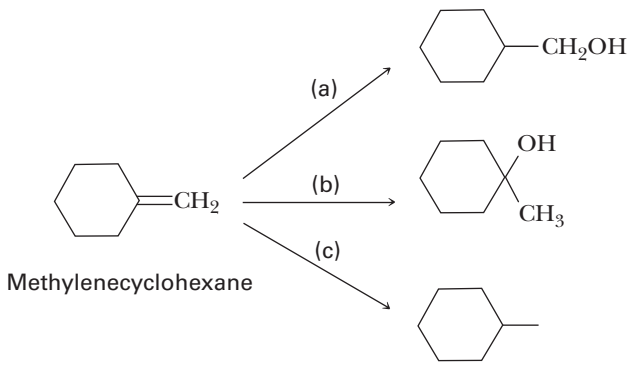
5.45 Show how to convert ethylene into these compounds:

(a) Ethane
(b) Ethanol
(c) Bromoethane
(d) 1,2-Dibromoethane
(e) Chloroethane
(f) 1-butene

5.46 Show how to convert cyclopentene into these compounds:



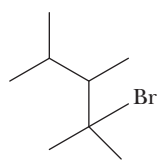
5.47 Show how to convert methylenecyclohexane into each of these compounds.

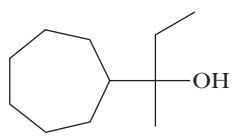


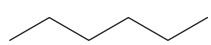
5.48 Show how to convert 1-butene into these compounds:

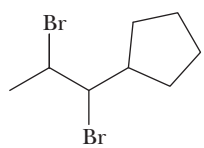
(a) Butane
(b) 2-Butanol
(c) 1-Butanol
(d) 2-Bromobutane
(e) 1,2-Dibromobutane
(f) 3-methylpentane

5.49 Show how the following compounds can be synthesized in good yields from an alkene:

(a) 

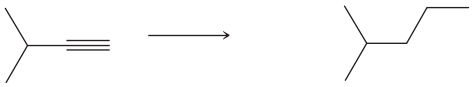
(b) 

(c) 

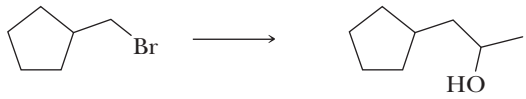
(d) 

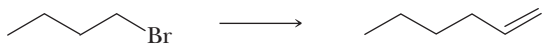
5.50 How would you prepare *cis*-3-hexene using only acetylene as the source of carbon atoms, and using any necessary inorganic regents? **(See Example 5.10)**

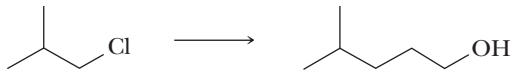
5.51 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. Note that some will require more than one step.

(a) 

(b) 

(c) 

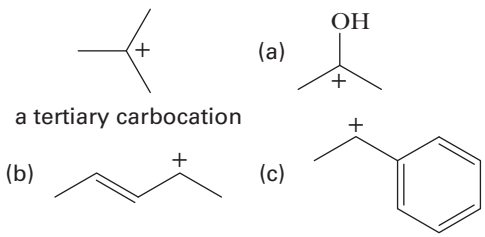
(d) 

(e) 

(f) 

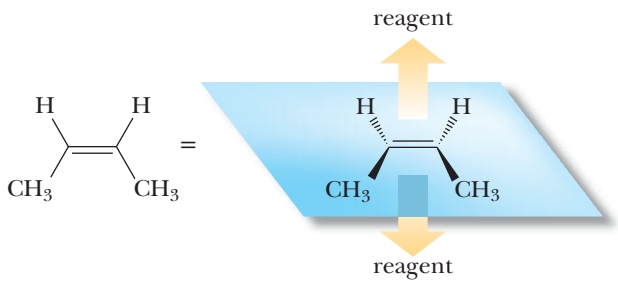
LOOKING AHEAD

5.52 Each of the following 2° carbocations is more stable than the tertiary-butyl carbocation shown:



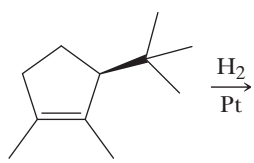
Provide an explanation for each cation's enhanced stability.

5.53 Recall that an alkene possesses a π cloud of electrons above and below the plane of the C=C bond. Any reagent can therefore react with either face of the double bond. Determine whether the reaction of each of the given reagents with the top face of *cis*-2-butene will produce the same product as the reaction of the same reagent with the bottom face. (*Hint*: Build molecular models of the products and compare them.)



(a) H_2/Pt (b) $\dfrac{\text{1) } BH_3 \cdot THF}{\text{2) NaOH, HOOH}}$ (c) Br_2/CH_2Cl_2

5.54 This reaction yields two products in differing amounts:



Draw the two products and predict which product is favored.

GROUP LEARNING ACTIVITIES

5.55 Take turns quizzing each other on the reactions presented in this chapter in the following ways:

(a) Say the name of a reaction and ask each other to come up with the reagents and products of that reaction. For example, if you say "catalytic hydrogenation of an alkene" the answer should be "H_2/Pt reacts to give an alkane."

(b) Describe a set of reagents and ask each other what functional group(s) the reagents react with. For example, if you say "H_2/Pt," the answer should be "alkenes" and "alkynes."

(c) Name a functional group or class of compound as a product of a reaction and ask what functional group or class of compound could be used to synthesize that product. For example, if you say "alkene," the answer should be "alkyne."

5.56 Using a piece of paper or, preferably, a whiteboard or chalkboard, take turns drawing the mechanisms of each reaction in this chapter from memory. If you forget a step or make a mistake, another member of the group should step in and finish it.

5.57 With the exception of ethylene to ethanol, the acid-catalyzed hydration of alkenes cannot be used for the synthesis of primary alcohols. Explain why this is so.

5.58 Discuss the following word problem by proposing structures and debating possible outcomes. Use a whiteboard or chalkboard if possible. Consider alkenes A, B, and C, each with molecular formula C_6H_{12}. A–C undergo catalytic reduction to give hexane as the only product. Acid-catalyzed hydration of A gives only one alcohol product. Acid-catalyzed hydration of B gives a mixture of two alcohols. Acid-catalyzed hydration of C gives only one alcohol. All alcohols are constitutional isomers with the molecular formula $C_6H_{14}O$.

(a) Propose structural formulas and names for A–C.

(b) Propose structural formulas for the product alcohols that are consistent with these experimental results.

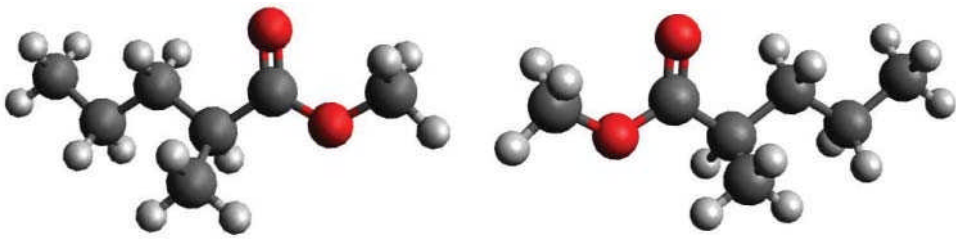
(c) Propose structural formulas for two other alkenes, each with the molecular formula C_6H_{12} that will also give only one alcohol upon acid-catalyzed hydration.

Chirality: The Handedness of Molecules

Valentyn Volkov/Shutterstock

6

Methyl 2-methylpentanoate is a flavor molecule that contributes to the fruity smell of apples. It exists in two forms that are mirror images of each other, but only one of these forms smells fruity. The other is nearly odorless to humans. Inset: Models of both mirror image forms of methyl 2-methylpentanoate



KEY QUESTIONS

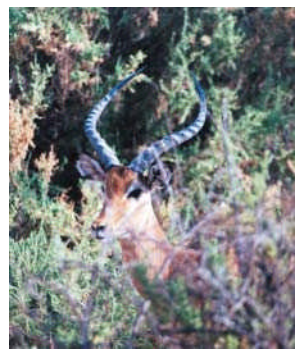
HOW TO

CHEMICAL CONNECTIONS

Mirror image The reflection of an object in a mirror.

IN THIS CHAPTER, we will explore the relationships between three-dimensional objects and their mirror images. When you look in a mirror, you see a reflection, or **mirror image**, of yourself. Now, suppose your mirror image becomes a three-dimensional object. We could then ask, "What is the relationship between you and your mirror image?" By relationship, we mean "Can your reflection be superposed on the original 'you' in such a way that every detail of the reflection corresponds exactly to the original?" The answer is that you and your mirror image are not superposable. If you have a ring on the little finger of your right hand, for example, your mirror image has the ring on the little finger of its left hand. If you part your hair on your right side, the part will be on the left side in your mirror image. Simply stated, you and your reflection are different objects. You cannot superpose one on the other.

An understanding of relationships of this type is fundamental to an understanding of organic chemistry and biochemistry. In fact, the ability to visualize molecules as three-dimensional objects is a survival skill in organic chemistry and biochemistry. We suggest that you purchase a set of molecular models. Alternatively you may have access to a computer lab with a modeling program. We urge you to use molecular models frequently as an aid to visualizing the spatial concepts in this and later chapters.

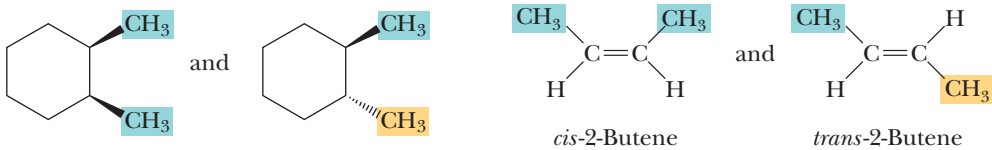


William H. Brown

The horns of this African gazelle show chirality and are mirror images of each other.

6.1 What Are Stereoisomers?

Stereoisomers have the same molecular formula and the same connectivity of atoms in their molecules, but different three-dimensional orientations of their atoms in space. The one example of stereoisomers we have seen thus far is that of *cis–trans* isomers in cycloalkanes (Section 3.7) and alkenes (Section 4.1C):



cis-1,2-Dimethylcyclohexane

trans-1,2-Dimethylcyclohexane

cis-2-Butene or *Z*-2-Butene

trans-2-Butene or *E*-2-Butene

Stereoisomers Isomers that have the same molecular formula and the same connectivity, but different orientations of their atoms in space.

In this chapter, we study two types of stereoisomers, enantiomers and diastereomers (Figure 6.1).

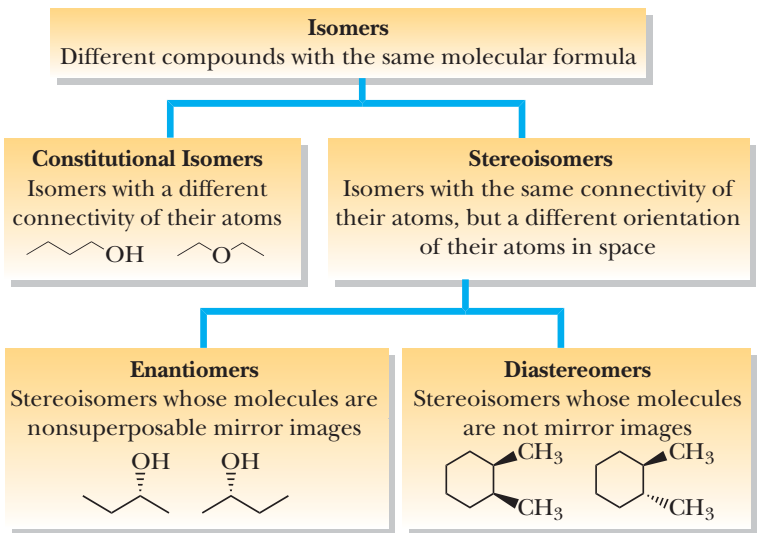


FIGURE 6.1 Relationships among isomers and some examples.

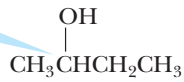
6.2 What Are Enantiomers?

Enantiomers are stereoisomers that are nonsuperposable mirror images. The significance of enantiomerism is that, except for inorganic and a few simple organic compounds, the vast majority of molecules in the biological world show this type of isomerism, including carbohydrates (Chapter 17), lipids (Chapter 19), amino acids and proteins (Chapter 18), and nucleic acids (DNA and RNA, Chapter 20). Further, approximately one-half of the medications used in human medicine also show this type of isomerism.

Enantiomers Stereoisomers that are nonsuperposable mirror images; the term refers to a relationship between pairs of objects.

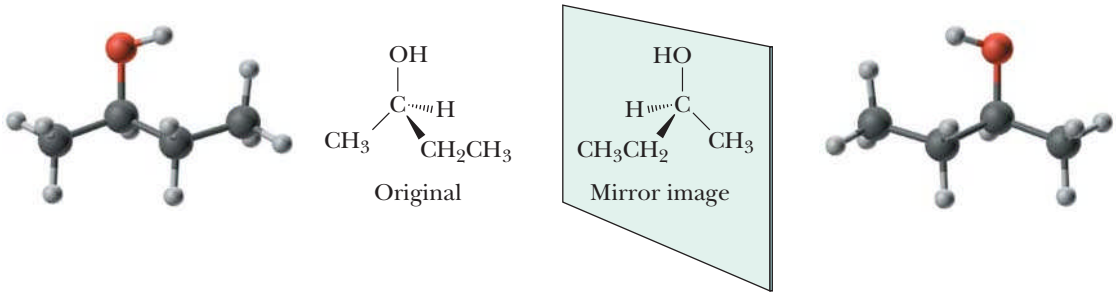
As an example of a molecule that exhibits enantiomerism, let us consider 2-butanol. As we go through the discussion of this molecule, we focus on carbon 2, the carbon bearing the —OH group. What makes this carbon of interest is that it has four different groups bonded to it. The most common cause of enantiomerism among organic molecules is a carbon bonded to four different groups.

the four different "groups" bonded to this carbon are —H, —OH, —CH_3, and —CH_2CH_3



2-Butanol

The structural formula we have just drawn does not show the shape of 2-butanol or the orientation of its atoms in space. To do this, we must consider the molecule as a three-dimensional object. On the left are a ball-and-stick model of 2-butanol and a perspective drawing of what we will call the "original" molecule. See Table 1.7 to review the meaning of the dashes and wedges in perspective drawings.



To the right in the preceding diagram is the mirror image of the original molecule. Every molecule and, in fact, every object in the world around us, has a mirror image. The question we now need to ask is "What is the relationship between the original representation of 2-butanol and its mirror image?" To answer this question, you need to imagine that you can pick up the mirror image and move it in space in any way you wish. If you can move the mirror image in space and find that it fits over the original so that every bond, atom, and detail of the mirror image exactly matches the bonds, atoms, and details of the original, then the two are **superposable**. In this case, the mirror image and the original represent the same molecule; they are only oriented differently in space. If, however, no matter how you turn the mirror image in space, it will not fit exactly on the original with every detail matching, then the two are **nonsuperposable**; they are different molecules.

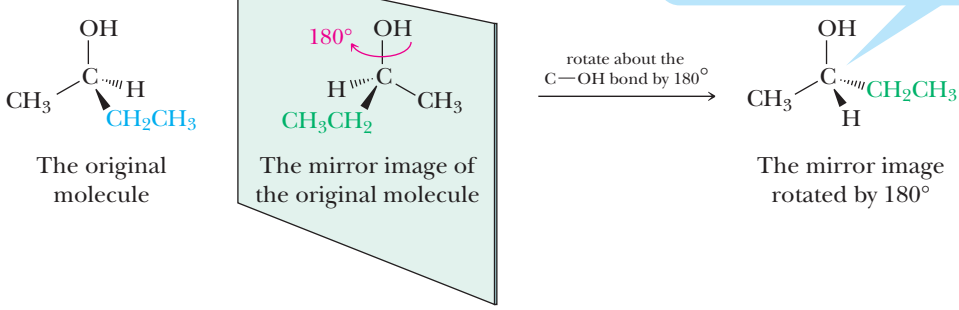
Superposable Able to be overlapped onto another object such that all features match exactly.

Nonsuperposable Not able to be overlapped onto another object such that all features match exactly.

The key point here is that either an object is superposable on its mirror image or it isn't. Now let us look at 2-butanol and its mirror image and ask, "Are they or are they not superposable?"

The following drawings illustrate one way to see that the mirror image of 2-butanol is not superposable on the original molecule:

after rotating 180° about the C—O bond, the CH_3—C—OH portion of the mirror image now corresponds to the same atoms of the original. However, the —H and —CH_2CH_3 groups are nonsuperposable because they extend in different directions in space



By rotating the mirror image as we did, its —OH and —CH_3 groups now fit exactly on top of the —OH and —CH_3 groups of the original. But the —H and —CH_2CH_3 groups of the two do not match: The —H is away from you in the original, but toward you in the mirror image; the —CH_2CH_3 group is toward you in the original, but away from you in the mirror image. We conclude that the original of 2-butanol and its mirror image are nonsuperposable and, therefore, are different compounds.

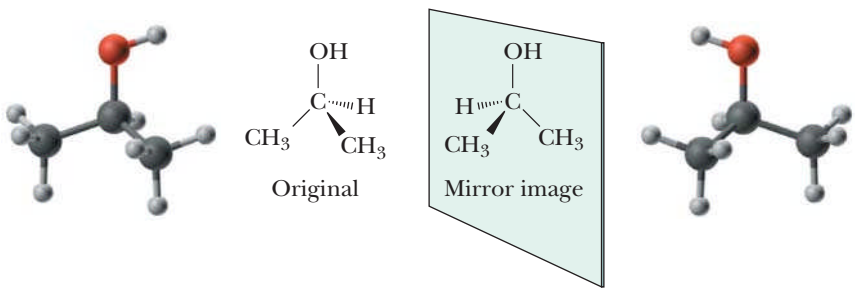
To summarize, we can rotate the mirror image of 2-butanol in space in any way we want, but as long as no bonds are broken or rearranged, only two of the four groups bonded to carbon-2 of the mirror image can be made to coincide with those on the original. Because 2-butanol and its mirror image are not superposable, they are enantiomers. Like gloves, enantiomers always occur in pairs.

Objects that are not superposable on their mirror images are said to be **chiral** (pronounced ki′ -ral, rhymes with spiral; from the Greek: *cheir*, hand); that is, they show handedness. Chirality is encountered in three-dimensional objects of all sorts. Your left hand is chiral, and so is your right hand. A spiral binding on a notebook is chiral. A machine screw with a right-handed twist is chiral. A ship's propeller is chiral. As you examine the objects in the world around you, you will undoubtedly conclude that the vast majority of them are chiral.

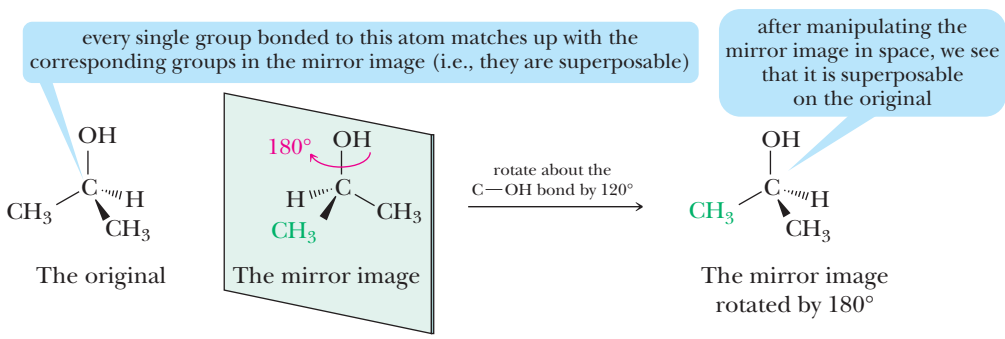
Chiral From the Greek *cheir*, meaning hand; chiral objects are not superposable on their mirror images.

As we said before we examined the original and the mirror image of 2-butanol, the most common cause of enantiomerism in organic molecules is the presence of a carbon with four different groups bonded to it. Let us examine this statement further by considering a molecule such as 2-propanol, which has no such carbon. In this molecule, carbon-2 is bonded to three different groups, but no carbon is bonded to four different groups. The question we ask is, "Is the mirror image of 2-propanol superposable on the original, or isn't it?"

In the following diagram, on the left is a three-dimensional representation of 2-propanol, and on the right is its mirror image:



The question we now ask is "What is the relationship of the mirror image to the original?" This time, let us rotate the mirror image by 120° about the C—OH bond and then compare it with the original. When we do this rotation, we see that all atoms and bonds of the mirror image fit exactly on the original. This means that the structures we first drew for the original and its mirror image are, in fact, the same molecule viewed from different perspectives:



If an object and its mirror image are superposable, then the object and its mirror image are identical, and there is no possibility of enantiomerism. We say that such an object is **achiral** (without chirality).

Charles D. Winters

Left- and right-handed sea shells. If you cup a right-handed shell in your right hand with your thumb pointing from the narrow end to the wide end, the opening will be on your right.

Achiral An object that lacks chirality; an object that has no handedness and is superposable on its mirror image.

Plane of symmetry An imaginary plane passing through an object and dividing it such that one half is the mirror image of the other half.

An achiral object has at least one plane of symmetry. A **plane of symmetry** (also called a *mirror plane*) is an imaginary plane passing through an object and dividing it so that one-half of the object is the reflection of the other half. The beaker shown in Figure 6.2 has a single plane of symmetry, whereas a cube has several planes of symmetry. 2-Propanol also has a single plane of symmetry.

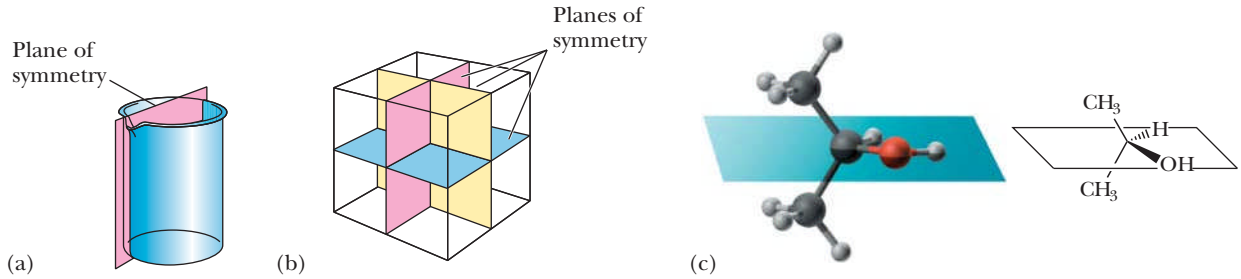


FIGURE 6.2 Planes of symmetry in (a) a beaker, (b) a cube, and (c) 2-propanol. The beaker and 2-propanol each have one plane of symmetry; the cube has several planes of symmetry, only three of which are shown in the figure.

Chiral center An atom, most commonly a carbon, with four different groups bonded to it.

Stereocenter An atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer.

To repeat, the most common cause of chirality in organic molecules is a tetrahedral carbon atom with four different groups bonded to it. We call such a carbon atom a **chiral center**. Chiral centers are one type of **stereocenter**, which describes an atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer. 2-Butanol has one stereocenter; 2-propanol has none.

As another example of a molecule with a stereocenter, consider 2-hydroxypropanoic acid, more commonly named lactic acid. Lactic acid is a product of anaerobic glycolysis and is what gives sour cream its sour taste. Figure 6.3 shows three-dimensional representations of lactic acid and its mirror image. In these representations, all bond angles about the central carbon atom are approximately 109.5°, and the four bonds projecting from it are directed toward the corners of a regular tetrahedron. Lactic acid shows enantiomerism; that is, it and its mirror image are not superposable, but rather are different molecules.

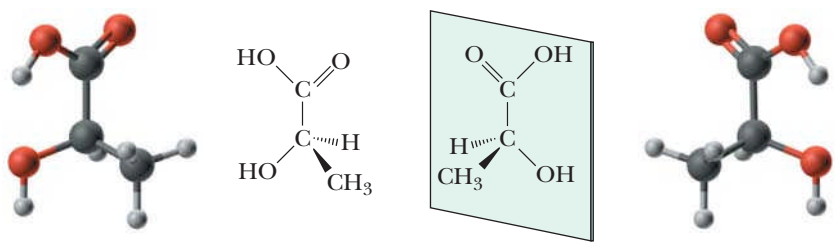
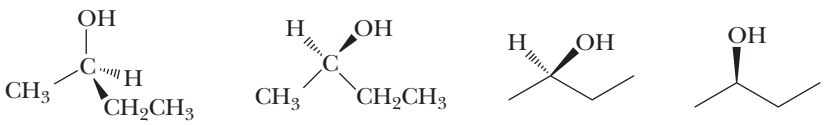


FIGURE 6.3 Three-dimensional representations of lactic acid and its mirror image.

HOW TO 6.1 Draw Enantiomers

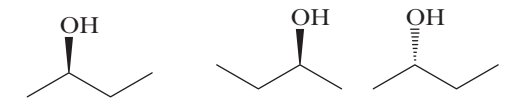
Now that we know what enantiomers are, we can think about how to represent their three-dimensional structures on a two-dimensional page. Let us take one of the enantiomers of 2-butanol as an example. Following are four different representations of this enantiomer:



(1) (2) (3) (4)

In our initial discussions of 2-butanol, we used (1) to show the tetrahedral geometry of the stereocenter; in it, two groups are in the plane of the paper, a third is coming out of the plane toward us, and the fourth is behind the plane, away from us. We can turn (1) slightly in space and tip it a bit to place the carbon framework in the

plane of the paper. Doing so gives us representation (2), in which we still have two groups in the plane of the paper, one coming toward us and one going away from us. For an even more abbreviated representation of this enantiomer of 2-butanol, we can turn (2) into the line-angle formula (3). Although we don't normally show hydrogens in a line-angle formula, we do so in (3) just to remind ourselves that the fourth group on this stereocenter is really there and that it is H. Finally, we can carry the abbreviation a step further and write 2-butanol as (4). Here, we omit the H on the stereocenter, but we know that it must be there (carbon needs four bonds), and we know that it must be behind the plane of the paper. Clearly, the abbreviated formulas (3) and (4) are the easiest to draw, and we will rely on these representations throughout the remainder of the text. When you have to draw three-dimensional representations of stereocenters, try to keep the carbon framework in the plane of the paper and the other two atoms or groups of atoms on the stereocenter toward and away from you, respectively. Using representation (4) as a model, we get the following two different representations of its enantiomer:

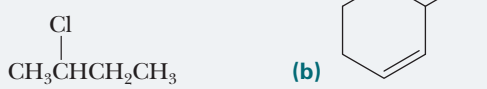


One enantiomer of 2-butanol — Alternative representations for its mirror image

Notice that in the first alternative, the carbon skeleton has been reversed.

EXAMPLE 6.1

Each of the following molecules has one stereocenter:



Identify the stereocenter in each and draw stereorepresentations of the enantiomers of each.

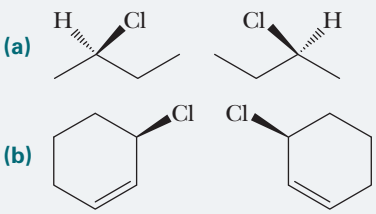
STRATEGY

When locating stereocenters, it is often helpful to draw in the hydrogens in line-angle drawings. Carbon atoms with only one or two lines extending from them, as well as sp^2 and *sp* hybridized carbons, can be excluded from consideration. Once the stereocenters are identified, use dashed and solid wedges to show the bonds to substituents.

See problems 6.15, 6.19–6.22

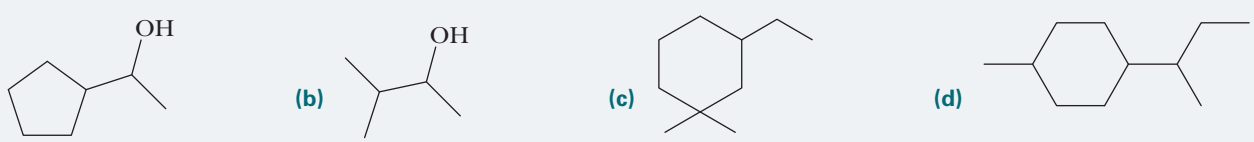
SOLUTION

You will find it helpful to study models of each pair of enantiomers and to view them from different perspectives. As you work with these models, notice that each enantiomer has a carbon atom bonded to four different groups, which makes the molecule chiral. Translate what you see in each model by using perspective drawings. The hydrogen at the stereocenter is shown in (a) but not in (b).



PROBLEM 6.1

Each of the following molecules has one stereocenter:

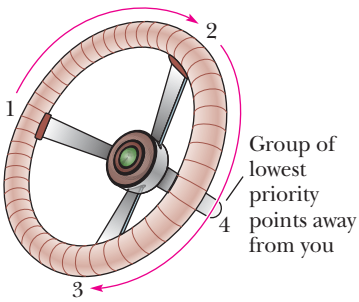


Identify the stereocenter in each and draw stereorepresentations of the enantiomers of each.

6.3 How Do We Designate the Configuration of a Stereocenter?

The over-the-counter medication Ibuprofen is sold as a mixture of enantiomers.

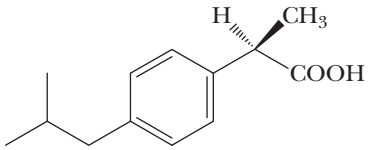
R,S system A set of rules for specifying the configuration about a stereocenter.



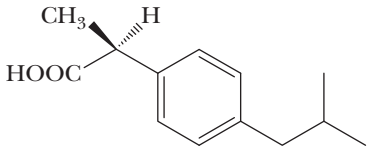
R From the Latin *rectus*, meaning right; used in the R,S system to show that the order of priority of groups on a stereocenter is clockwise.

S From the Latin *sinister*, meaning left; used in the R,S system to show that the order of priority of groups on a stereocenter is counterclockwise.

Because enantiomers are different compounds, each must have a different name. The over-the-counter drug ibuprofen, for example, shows enantiomerism and can exist as the pair of enantiomers shown here:



The inactive enantiomer of Ibuprofen



The active enantiomer

Only one enantiomer of ibuprofen is biologically active. This enantiomer reaches therapeutic concentrations in the human body in approximately 12 minutes. However, in this case, the inactive enantiomer is not wasted. The body converts it to the active enantiomer, but that takes time.

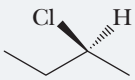
What we need is a way to name each enantiomer of ibuprofen (or any other pair of enantiomers for that matter) so that we can refer to them in conversation or in writing. To do so, chemists have developed the **R,S system**. The first step in assigning an R or S configuration to a stereocenter is to arrange the groups bonded to it in order of priority. For this, we use the same set of **priority rules** we used in Section 4.2C to assign an E,Z configuration to an alkene.

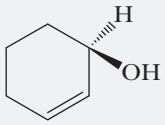
To assign an R or S configuration to a stereocenter,

1. Locate the stereocenter, identify its four substituents, and assign a priority from 1 (highest) to 4 (lowest) to each substituent.
2. Orient the molecule in space so that the group of lowest priority (4) is directed away from you, as would be, for instance, the steering column of a car. The three groups of higher priority (1–3) then project toward you, as would the spokes of a steering wheel.
3. Read the three groups projecting toward you in order, from highest priority (1) to lowest priority (3).
4. If reading the groups proceeds in a clockwise direction, the configuration is designated **R** (Latin: *rectus*, straight, correct); if reading proceeds in a counterclockwise direction, the configuration is **S** (Latin: *sinister*, left). You can also visualize this situation as follows: Turning the steering wheel to the right equals R, and turning it to the left equals S.

EXAMPLE 6.2

Assign an R or S configuration to each stereocenter:

(a) 

(b) 

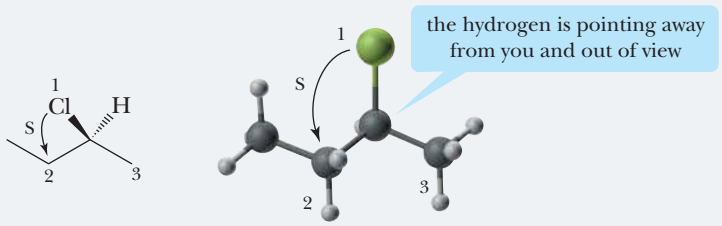
STRATEGY

First determine the priorities of the groups bonded to the stereocenter. If necessary reorient the molecule so that the group of lowest priority is away from you. Then read the R/S configuration by going from highest to lowest priority.

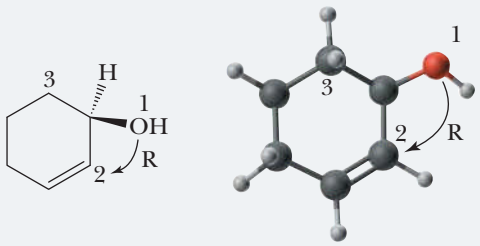
SOLUTION

View each molecule through the stereocenter and along the bond from the stereocenter toward the group of lowest priority.

(a) The order of priority is —Cl > —CH_2CH_3 > —CH_3 > —H. The group of lowest priority, H, points away from you. Reading the groups in the order 1, 2, 3 occurs in the counterclockwise direction, so the configuration is S.



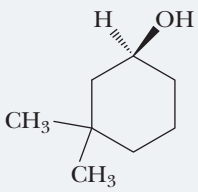
(b) The order of priority is —OH > —CH=CH > —CH_2 —CH_2 > —H. With hydrogen, the group of lowest priority, pointing away from you, reading the groups in the order 1, 2, 3 occurs in the clockwise direction, so the configuration is R.

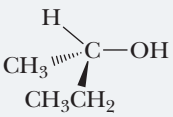


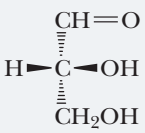
See problems 6.24–6.27, 6.29, 6.39

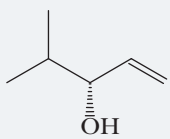
PROBLEM 6.2

Assign an R or S configuration to each stereocenter:

(a) 

(b) 

(c) 

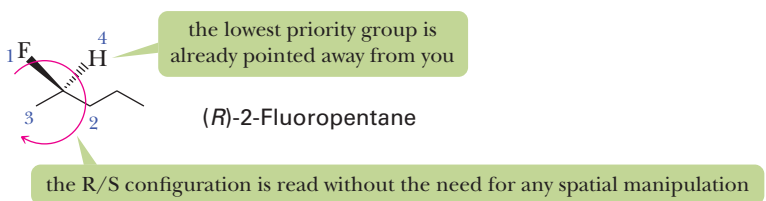
(d) 

HOW TO 6.2 Determine the R & S Configuration without Rotating the Molecule

If you are having difficulty visualizing the spatial rotation of perspective drawings, the following techniques may be of use.

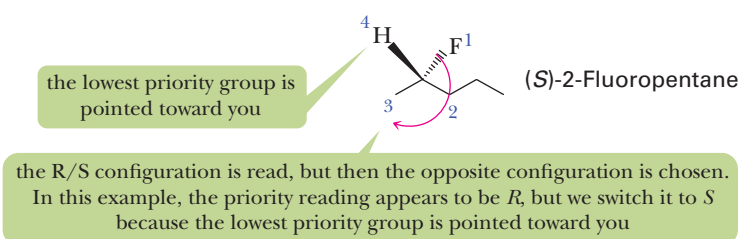
SCENARIO 1: *The lowest priority group is already directed away from you.*

If the perspective drawing contains the lowest priority group on a dashed bond, it is a simple matter of reading the other three groups from highest to lowest priority.



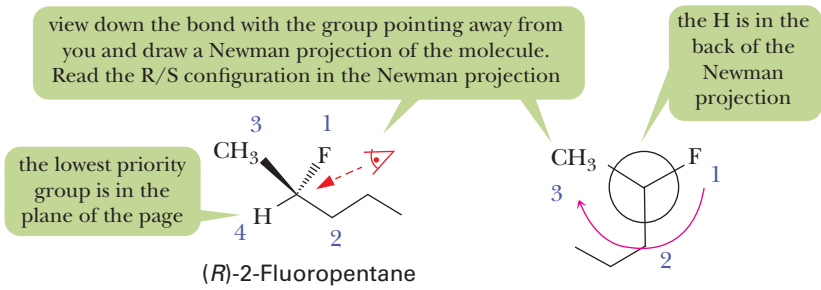
SCENARIO 2: *The lowest priority group is directed toward you.*

If the perspective drawing contains the lowest priority group on a wedged bond, read the priority of the other three groups, but assign a configuration that is opposite to what is actually read.



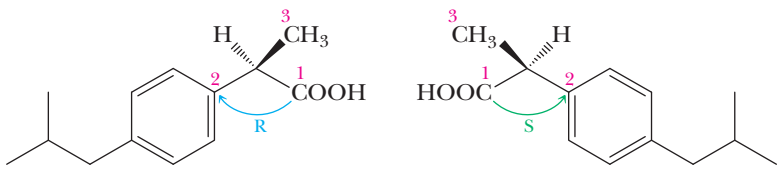
SCENARIO 3: *The lowest priority group is in the plane of the page.*

If the perspective drawing contains the lowest priority group in the plane of the page, view down the bond connecting the group to the stereocenter and draw a Newman projection (Section 3.6A).



(*R*)-2-Fluoropentane

Now let us return to our three-dimensional drawing of the enantiomers of ibuprofen and assign each an R or S configuration. In order of decreasing priority, the groups bonded to the stereocenter are —COOH > —C_6H_4 > —CH_3 > H. In the enantiomer on the left, reading the groups on the stereocenter in order of priority occurs clockwise. Therefore, this enantiomer is (*R*)-ibuprofen, and its mirror image is (*S*)-ibuprofen:



(*R*)-Ibuprofen
(the inactive enantiomer)

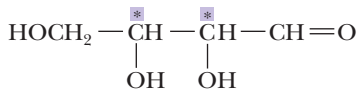
(*S*)-Ibuprofen
(the active enantiomer)

6.4 What Is the 2^n Rule?

Now let us consider molecules with two stereocenters. To generalize, for a molecule with ***n*** stereocenters, the maximum number of stereoisomers possible is $\mathbf{2}^{\boldsymbol{n}}$. We have already verified that, for a molecule with one stereocenter, $2^1 = 2$ stereoisomers (one pair of enantiomers) are possible. For a molecule with two stereocenters, $2^2 = 4$ stereoisomers are possible; for a molecule with three stereocenters, $2^3 = 8$ stereoisomers are possible, and so forth.

A. Enantiomers and Diastereomers

We begin our study of molecules with two stereocenters by considering 2,3,4-trihydroxybutanal. Its two stereocenters are marked with asterisks:



2,3,4-Trihydroxybutanal

The maximum number of stereoisomers possible for this molecule is $2^2 = 4$, each of which is drawn in Figure 6.4.

Stereoisomers (a) and (b) are nonsuperposable mirror images and are, therefore, a pair of enantiomers. Stereoisomers (c) and (d) are also nonsuperposable mirror images and are a second pair of enantiomers. We describe the four stereoisomers of 2,3,4-trihydroxybutanal by saying that they consist of two pairs of enantiomers. Enantiomers (a) and (b) are named **erythrose**, which is synthesized in erythrocytes (red blood cells)—hence the name. Enantiomers (c) and (d) are named **threose**. Erythrose and threose belong to the class of compounds called carbohydrates, which we discuss in Chapter 17.

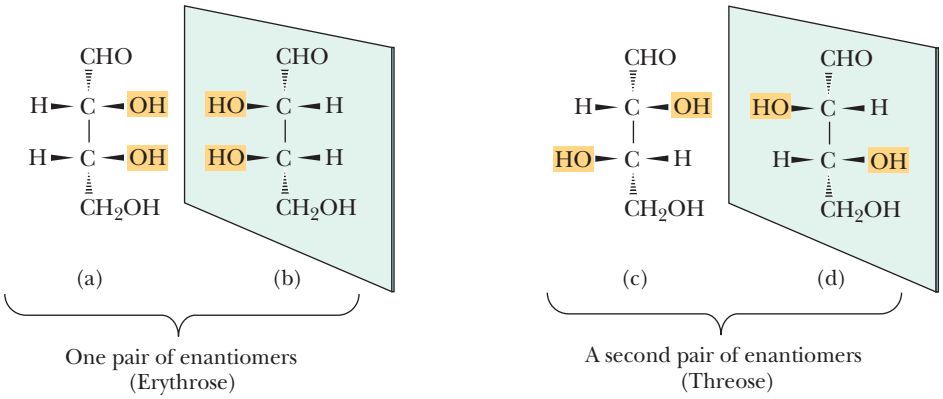


FIGURE 6.4 The four stereoisomers of 2,3,4-trihydroxybutanal, a compound with two stereocenters. Configurations (a) and (b) are (2*R*,3*R*) and (2*S*,3*S*), respectively. Configurations (c) and (d) are (2*R*,3*S*) and (2*S*,3*R*), respectively.

We have specified the relationship between (a) and (b) and between (c) and (d). What is the relationship between (a) and (c), between (a) and (d), between (b) and (c), and between (b) and (d)? The answer is that they are diastereomers. **Diastereomers** are stereoisomers that are not enantiomers; that is, they are stereoisomers that are not mirror images of each other.

Diastereomers Stereoisomers that are not mirror images of each other; the term refers to relationships among objects.

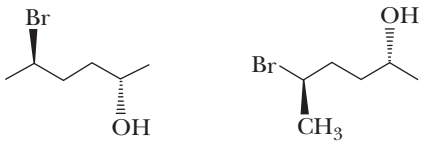
Determine Whether Two Compounds Are the Same, Enantiomers, or Diastereomers without the Need to Spatially Manipulate the Molecule

HOW TO 6.3

If you are having difficulty visualizing the spatial rotation of perspective drawings, the following technique may be of use.

STEP 1: *Verify that the compounds are stereoisomers.*

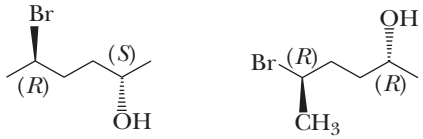
Make sure that the two compounds in question have the same molecular formula and the same connectivity of atoms.



Chemical Formula for both: $C_6H_{13}BrO$
Both have a 6-carbon chain with Br at the 5 position and OH at the 2 position

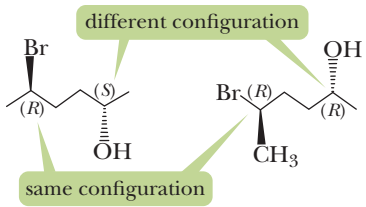
STEP 2: *Assign R/S configurations to each stereocenter in both compounds.*

See HowTo 6.2 for instructions.



STEP 3: *Compare the configuration at corresponding stereocenters.*

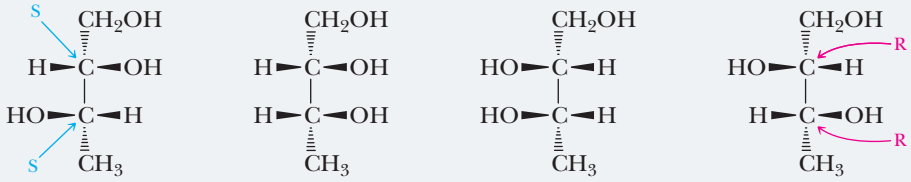
If the configurations match, the compounds are identical. If the configurations are opposite at each corresponding stereocenter, the compounds are enantiomers. Any other scenario indicates that the compounds are diastereomers.



Possible Scenario	Relationship
all configurations the same	identical compounds
all configurations opposite	enantiomers
any other scenario	diastereomers

EXAMPLE 6.3

Following are stereorepresentations of the four stereoisomers of 1,2,3-butanetriol:



Configurations are given for the stereocenters in (1) and (4).

(a) Which compounds are enantiomers? **(b)** Which compounds are diastereomers?

STRATEGY

Determine the R/S configuration of the stereocenters in each compound and compare corresponding stereocenters to determine their relationship (see HowTo 6.3).

SOLUTION

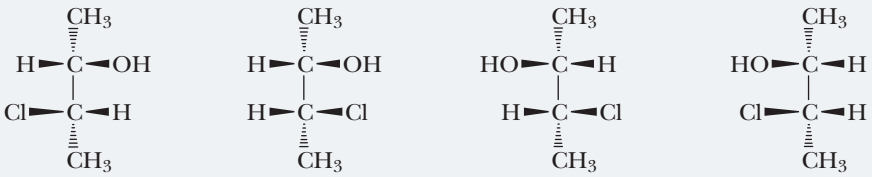
(a) Compounds (1) and (4) are one pair of enantiomers, and compounds (2) and (3) are a second pair of enantiomers. Note that the configurations of the stereocenters in (1) are the opposite of those in (4), its enantiomer.

(b) Compounds (1) and (2), (1) and (3), (2) and (4), and (3) and (4) are diastereomers.

See problem 6.23

PROBLEM 6.3

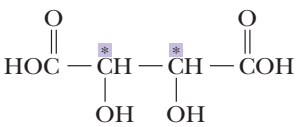
Following are stereorepresentations of the four stereoisomers of 3-chloro-2-butanol:



(a) Which compounds are enantiomers? **(b)** Which compounds are diastereomers?

B. Meso Compounds

Certain molecules containing two or more stereocenters have special symmetry properties that reduce the number of stereoisomers to fewer than the maximum number predicted by the 2^n rule. One such molecule is 2,3-dihydroxybutanedioic acid, more commonly named tartaric acid:



2,3-Dihydroxybutanedioic acid
(Tartaric acid)

Tartaric acid is a colorless, crystalline compound occurring largely in the vegetable kingdom, especially in grapes. During the fermentation of grape juice, potassium bitartrate (one —COOH group is present as a potassium salt, $—COO^- K^+$) deposits as a crust on the sides of wine casks. Then, collected and purified, it is sold commercially as cream of tartar.

Carbons 2 and 3 of tartaric acid are stereocenters, and, from the 2^n rule, the maximum number of stereoisomers possible is $2^2 = 4$. Figure 6.5 shows the two pairs of mirror images of this compound. Structures (a) and (b) are nonsuperposable mirror images and, therefore, are a pair of enantiomers. Structures (c) and (d) are also mirror images, but they are superposable. To see this, imagine that you rotate (d) by 180° in the plane of the paper, lift it out of the plane of the paper, and place it on top of (c). If you do this mental manipulation correctly, you will find that (d) is superposable on (c). Therefore, (c) and (d) are *not* different molecules; they are the same molecule, just oriented differently. Because (c) and its mirror image are superposable, (c) is achiral.

Another way to verify that (c) is achiral is to see that it has a plane of symmetry that bisects the molecule in such a way that the top half is the reflection of the bottom half.

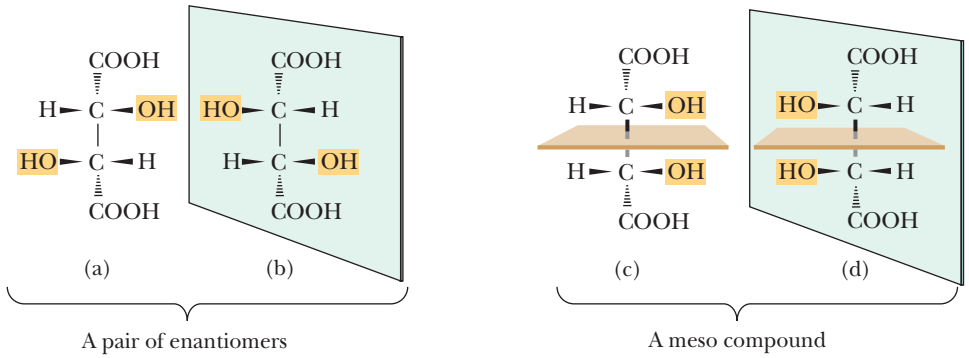


FIGURE 6.5 Stereoisomers of tartaric acid. One pair of enantiomers and one meso compound. The presence of an internal plane of symmetry indicates that the molecule is achiral.

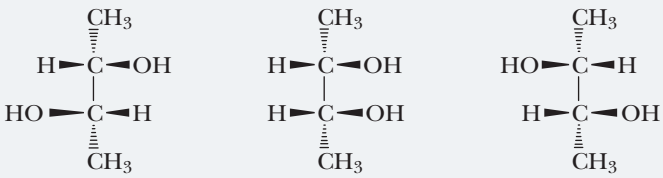
Thus, even though (c) has two stereocenters, it is achiral. The stereoisomer of tartaric acid represented by (c) or (d) is called a **meso compound**, defined as an achiral compound that contains two or more stereocenters.

Meso compound An achiral compound possessing two or more stereocenters.

We can now return to the original question: How many stereoisomers are there of tartaric acid? The answer is three: one meso compound and one pair of enantiomers. Note that the meso compound is a diastereomer of each of the other stereoisomers.

EXAMPLE 6.4

Following are stereorepresentations of the three stereoisomers of 2,3-butanediol:



(a) Which are enantiomers? **(b)** Which is the meso compound? **(c)** Which are diastereomers?

STRATEGY

Enantiomers are nonsuperposable mirror images. A meso compound is an achiral compound with two or more stereocenters, that is, a compound with two or more stereocenters that has a superposable mirror image.

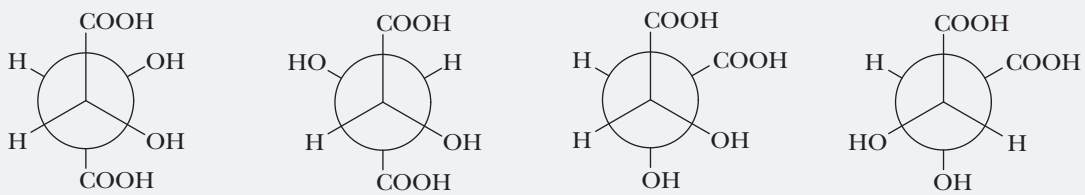
SOLUTION

(a) Compounds (1) and (3) are enantiomers.
(b) Compound (2) has an internal plane of symmetry and, therefore, is a meso compound.
(c) Pairs (1) and (2) and pairs (2) and (3) are diastereomers.

See problems 6.23, 6.36, 6.38

PROBLEM 6.4

Following are four Newman projection formulas for tartaric acid:



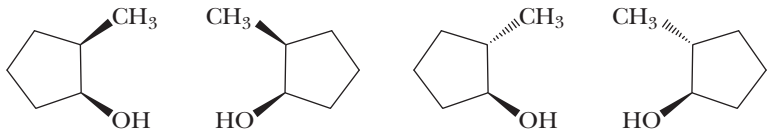
(a) Which represent the same compound? **(b)** Which represent enantiomers? **(c)** Which represent(s) meso-tartaric acid? **(d)** Which are diastereomers?

6.5 How Do We Describe the Chirality of Cyclic Molecules with Two Stereocenters?

In this section, we concentrate on derivatives of cyclopentane and cyclohexane that contain two stereocenters. We can analyze chirality in these cyclic compounds in the same way we analyzed it in acyclic compounds.

A. Disubstituted Derivatives of Cyclopentane

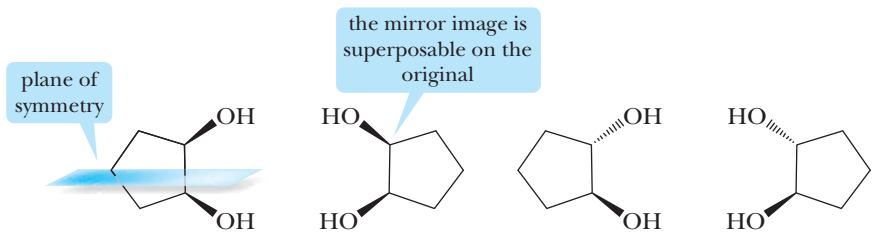
Let us start with 2-methylcyclopentanol, a compound with two stereocenters. Using the 2^n rule, we predict a maximum of $2^2 = 4$ stereoisomers. Both the *cis* isomer and the *trans* isomer are chiral. The *cis* isomer exists as one pair of enantiomers, and the *trans* isomer exists as a second pair:



cis-2-Methylcyclopentanol (a pair of enantiomers)

trans-2-Methylcyclopentanol (a pair of enantiomers)

1,2-Cyclopentanediol also has two stereocenters; therefore, the 2^n rule predicts a maximum of $2^2 = 4$ stereoisomers. As seen in the following stereodrawings, only three stereoisomers exist for this compound:



cis-1,2-Cyclopentanediol (a meso compound)

trans-1,2-Cyclopentanediol (a pair of enantiomers)

The *cis* isomer is achiral (meso) because it and its mirror image are superposable. The *cis* isomer is also achiral because it possesses a plane of symmetry that bisects the molecule into two mirror-image halves. The *trans* isomer is chiral and exists as a pair of enantiomers.

EXAMPLE 6.5

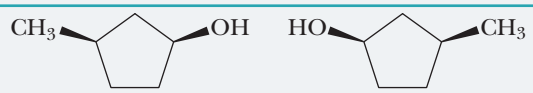
How many stereoisomers exist for 3-methylcyclopentanol?

STRATEGY

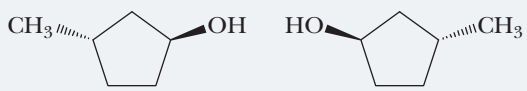
First identify all possible stereocenters, draw all possible pairs of stereoisomers, and determine which, if any, of the possible pairs of stereoisomers are meso compounds.

SOLUTION

There are two stereocenters in this compound and, therefore, four stereoisomers of 3-methylcyclopentanol. The *cis* isomer exists as one pair of enantiomers and the *trans* isomer as a second pair:



cis-3-Methylcyclopentanol (a pair of enantiomers)



trans-3-Methylcyclopentanol (a pair of enantiomers)

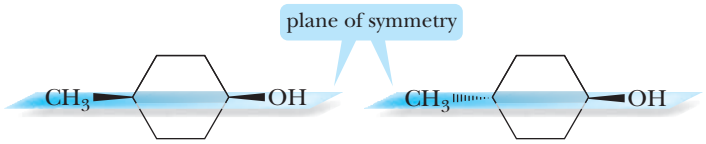
See problems 6.31, 6.33–6.35, 6.38, 6.39

PROBLEM 6.5

How many stereoisomers exist for 1,3-cyclopentanediol?

B. Disubstituted Derivatives of Cyclohexane

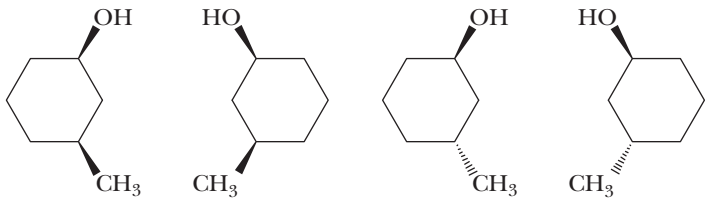
As an example of a disubstituted cyclohexane, let us consider the methylcyclohexanols. 4-Methylcyclohexanol can exist as two stereoisomers—a pair of *cis*–*trans* isomers:



cis-4-Methylcyclohexanol *trans*-4-Methylcyclohexanol

Both the *cis* and the *trans* isomers are achiral. In each, a plane of symmetry runs through the CH_3 and OH groups and the two attached carbons.

3-Methylcyclohexanol has two stereocenters and exists as $2^2 = 4$ stereoisomers, with the *cis* isomer existing as one pair of enantiomers and the *trans* isomer as a second pair:



cis-3-Methylcyclohexanol (a pair of enantiomers) *trans*-3-Methylcyclohexanol (a pair of enantiomers)

EXAMPLE 6.6

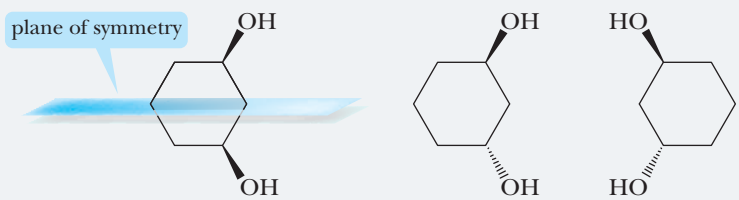
How many stereoisomers exist for 1,3-cyclohexanediol?

STRATEGY

Locate all stereocenters and use the 2^n rule to determine the maximum number of stereoisomers possible. Determine which, if any, of the possible stereoisomers are meso compounds.

SOLUTION

1,3-Cyclohexanediol has two stereocenters, and, according to the 2^n rule, a maximum of $2^2 = 4$ stereoisomers is possible. The *trans* isomer of this compound exists as a pair of enantiomers. The *cis* isomer has a plane of symmetry and is a meso compound. Therefore, although the 2^n rule predicts a maximum of four stereoisomers for 1,3-cyclohexanediol, only three exist—one pair of enantiomers and one meso compound:



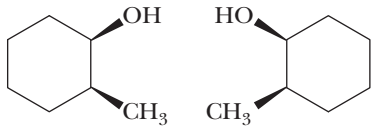
cis-1,3-Cyclohexanediol (a meso compound) *trans*-1,3-Cyclohexanediol (a pair of enantiomers)

See problems 6.31, 6.33–6.35, 6.38, 6.39

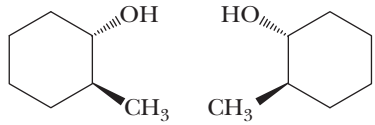
PROBLEM 6.6

How many stereoisomers exist for 1,4-cyclohexanediol?

Similarly, 2-methylcyclohexanol has two stereocenters and exists as $2^2 = 4$ stereoisomers, with the *cis* isomer existing as one pair of enantiomers and the *trans* isomer as a second pair:



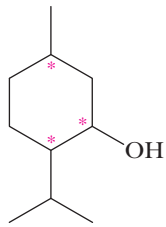
cis-2-Methylcyclohexanol
(a pair of enantiomers)



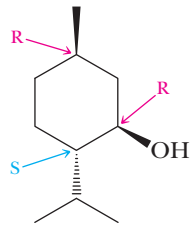
trans-2-Methylcyclohexanol
(a pair of enantiomers)

6.6 How Do We Describe the Chirality of Molecules with Three or More Stereocenters?

The 2^n rule applies equally well to molecules with three or more stereocenters. Here is a disubstituted cyclohexanol with three stereocenters, each marked with an asterisk:



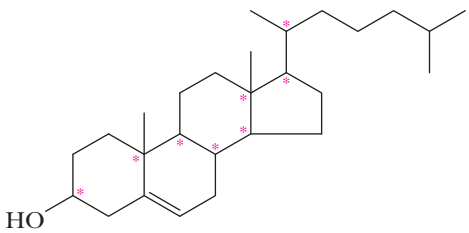
2-Isopropyl-5-methyl-
cyclohexanol



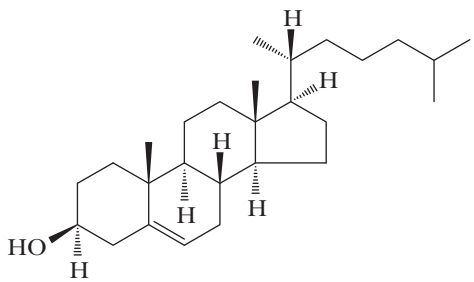
Menthol

There is a maximum of $2^3 = 8$ stereoisomers possible for this molecule. Menthol, one of the eight, has the configuration shown on the right. The configuration at each stereocenter is indicated. Menthol is present in peppermint and other mint oils.

Cholesterol, a more complicated molecule, has eight stereocenters:



Cholesterol has 8 stereocenters;
256 stereoisomers are possible



This is the stereoisomer found in
human metabolism

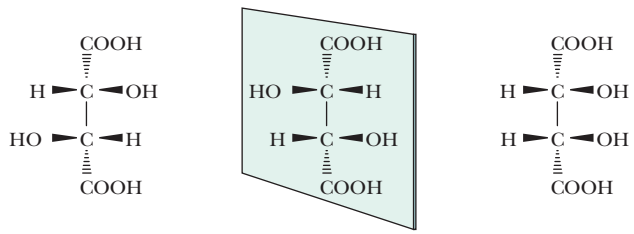
To identify the stereocenters, remember to add an appropriate number of hydrogens to complete the tetravalence of each carbon you think might be a stereocenter.

6.7 What Are the Properties of Stereoisomers?

Enantiomers have identical physical and chemical properties in achiral environments. The enantiomers of tartaric acid (Table 6.1), for example, have the same melting point, the same boiling point, the same solubilities in water and other common solvents, and the same values of pK_a (the acid ionization constant), and they all undergo the same acid–base reactions. The enantiomers of tartaric acid do, however, differ in optical activity (the ability to rotate the plane of polarized light), a property that is discussed in the next section.

Diastereomers have different physical and chemical properties, even in achiral environments. Meso-tartaric acid has different physical properties from those of the enantiomers.

TABLE 6.1 Some Physical Properties of the Stereoisomers of Tartaric Acid



	(*R,R*)-Tartaric acid	(*S,S*)-Tartaric acid	Meso-tartaric acid
Specific rotation*	+12.7	−12.7	0
Melting point (°C)	171–174	171–174	146–148
Density at 20 °C (g/cm^3)	1.7598	1.7598	1.660
Solubility in water at 20 °C (g/100 mL)	139	139	125
pK_1 (25 °C)	2.98	2.98	3.23
pK_2 (25 °C)	4.34	4.34	4.82

*Specific rotation is discussed in the next section.

6.8 How Is Chirality Detected in the Laboratory?

As we have already established, enantiomers are different compounds, and we must expect, therefore, that they differ in some property or properties. One property that differs between enantiomers is their effect on the plane of polarized light. Each member of a pair of enantiomers rotates the plane of polarized light, and for this reason, enantiomers are said to be **optically active**. To understand how optical activity is detected in the laboratory, we must first understand plane-polarized light and a polarimeter, the instrument used to detect optical activity.

Optically active Showing that a compound rotates the plane of polarized light.

A. Plane-Polarized Light

Ordinary light consists of waves vibrating in all planes perpendicular to its direction of propagation (Figure 6.6). Certain materials, such as calcite and Polaroid™ sheet (a plastic film containing properly oriented crystals of an organic substance embedded in it), selectively transmit light waves vibrating in parallel planes. Electromagnetic radiation vibrating in only parallel planes is said to be **plane polarized**.

Plane polarized Light vibrating only in parallel planes.

B. A Polarimeter

A **polarimeter** consists of a light source, a polarizing filter and an analyzing filter (each made of calcite or Polaroid™ film), and a sample tube (Figure 6.6). If the sample tube is empty, the intensity of light reaching the detector (in this case, your eye) is at its maximum when the polarizing axes of the two filters are parallel. If the analyzing filter is turned either clockwise or counterclockwise, less light is transmitted. When the axis of the analyzing filter is at right angles to the axis of the polarizing filter, the field of view is dark. This position of the analyzing filter is taken to be 0° on the optical scale.

Richard Megna, 1992/ Fundamental Photographs

A polarimeter is used to measure the rotation of plane-polarized light as it passes through a sample.

The ability of molecules to **rotate the plane of polarized light** can be observed with the use of a polarimeter in the following way: First, a sample tube filled with solvent is placed in the polarimeter, and the analyzing filter is adjusted so that no light passes through to the observer; that is, the filter is set to 0°. Then we place a solution of an optically active compound in the sample tube. When we do so, we find that a certain amount of light now passes through the analyzing filter. We also find that the plane of polarized light from the polarizing filter has been rotated so that it is no longer at an angle of 90° to the analyzing filter. Consequently, we rotate the analyzing filter to restore darkness in the field of view. The number of degrees, α, through which we must rotate the analyzing filter to restore darkness to the field of view is called the **observed rotation**. If we must turn the

Polarimeter An instrument for measuring the ability of a compound to rotate the plane of polarized light.

Observed rotation The number of degrees through which a compound rotates the plane of polarized light.

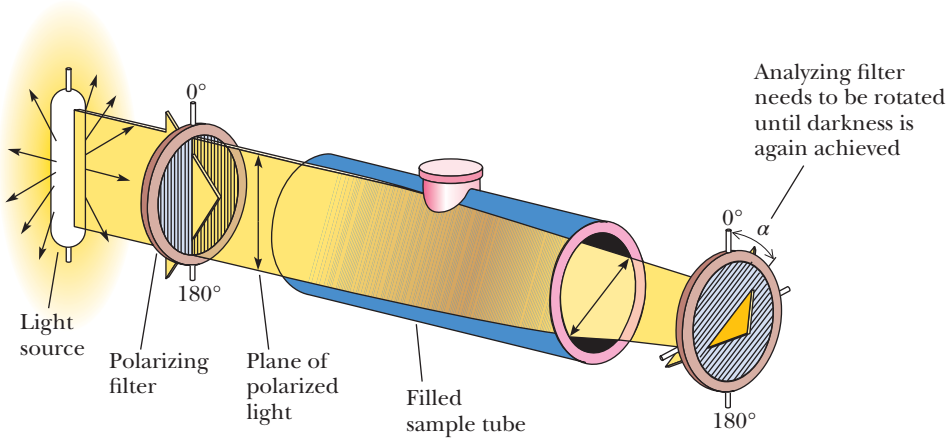


FIGURE 6.6 Schematic diagram of a polarimeter with its sample tube containing a solution of an optically active compound. The analyzing filter has been turned clockwise by α degrees to restore the dark field.

Dextrorotatory Rotating the plane of polarized light in a polarimeter to the right.

Levorotatory Rotating the plane of polarized light in a polarimeter to the left.

Specific rotation Observed rotation of the plane of polarized light when a sample is placed in a tube 1.0 dm long at a concentration of 1.0 g/mL.

analyzing filter to the right (clockwise) to restore the dark field, we say that the compound is **dextrorotatory** (Latin: *dexter*, on the right side); if we must turn it to the left (counterclockwise), we say that the compound is **levorotatory** (Latin: *laevus*, on the left side).

The magnitude of the observed rotation for a particular compound depends on its concentration, the length of the sample tube, the temperature, the solvent, and the wavelength of the light used. The **specific rotation**, $[\alpha]$, is defined as the observed rotation at a specific cell length and sample concentration expressed in grams per milliliter.

$$\text{specific rotation} = [\alpha]_{\lambda}^{T} = \frac{\text{observed rotation (degrees)}}{\text{Lengh (dm)} \times \text{concentration}}$$

The standard cell length is 1 decimeter (1 dm = 0.1 m). For a pure liquid sample, the concentration is expressed in grams per milliliter (g/mL; density). The temperature (T, in degrees centigrade) and wavelength (λ, in nanometers) of light are designated, respectively, as superscripts and subscripts. The light source most commonly used in polarimetry is the sodium D line (λ = 589 nm), the same line responsible for the yellow color of sodium-vapor lamps.

In reporting either observed or specific rotation, it is common to indicate a dextrorotatory compound with a plus sign in parentheses, (+), and a levorotatory compound with a minus sign in parentheses, (−). For any pair of enantiomers, one enantiomer is dextrorotatory and the other is levorotatory. For each member, the value of the specific rotation is exactly the same, but the sign is opposite. Following are the specific rotations of the enantiomers of 2-butanol at 25°C, observed with the D line of sodium:

(*S*)-(+)-2-Butanol $[\alpha]_{D}^{25}$ +13.52°

(*R*)-(−)-2-Butanol $[\alpha]_{D}^{25}$ −13.52°

C. Racemic Mixtures

Racemic mixture A mixture of equal amounts of two enantiomers.

Optically inactive Showing that a compound or mixture of compounds does not rotate the plane of polarized light.

An equimolar mixture of two enantiomers is called a **racemic mixture**, a term derived from the name "racemic acid" (Latin: *racemus*, a cluster of grapes), originally given to an equimolar mixture of the enantiomers of tartaric acid (Table 6.1). Because a racemic mixture contains equal numbers of the dextrorotatory and the levorotatory molecules, its specific rotation is zero. Alternatively, we say that a racemic mixture is **optically inactive**. A racemic mixture is indicated by adding the prefix (±) to the name of the compound.

6.9 What Is the Significance of Chirality in the Biological World?

Except for inorganic salts and a relatively few low-molecular-weight organic substances, the molecules in living systems, both plant and animal, are chiral. Although these molecules can exist as a number of stereoisomers, almost invariably only one stereoisomer is found in

nature. Of course, instances do occur in which more than one stereoisomer is found, but these rarely exist together in the same biological system.

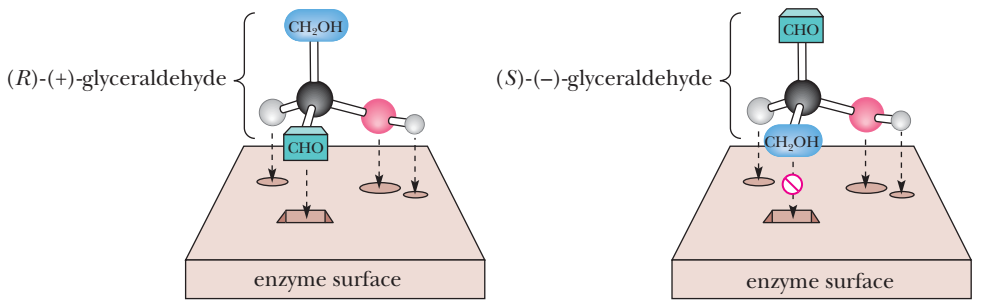
A. Chirality in Biomolecules

Perhaps the most conspicuous examples of chirality among biological molecules are the enzymes, all of which have many stereocenters. An example is chymotrypsin, an enzyme found in the intestines of animals. This enzyme catalyzes the digestion of proteins (Section 19.5). Chymotrypsin has 251 stereocenters. The maximum number of stereoisomers possible is thus 2^{251}, a staggeringly large number, almost beyond comprehension. Fortunately, nature does not squander its precious energy and resources unnecessarily: Only one of these stereoisomers of chymotrypsin is produced and used by any given organism.

Because enzymes are chiral substances, most either produce or react with only substances that match their stereochemical requirements.

B. How an Enzyme Distinguishes between a Molecule and Its Enantiomer

An enzyme catalyzes a biological reaction of a molecule by first positioning it at a **binding site** on the enzyme's surface. An enzyme with binding sites specific for three of the four groups on a stereocenter can distinguish between a molecule and its enantiomer or one of its diastereomers. Assume, for example, that an enzyme involved in catalyzing a reaction of glyceraldehyde has on its surface a binding site specific for —H, a second specific for —OH, and a third specific for —CHO. Assume further that the three sites are arranged on the enzyme surface as shown in Figure 6.7. The enzyme can distinguish (*R*)-(+)-glyceraldehyde (the natural, or biologically active, form) from its enantiomer because the natural enantiomer can be absorbed, with three groups interacting with their appropriate binding sites; for the S enantiomer, at best only two groups can interact with these binding sites.

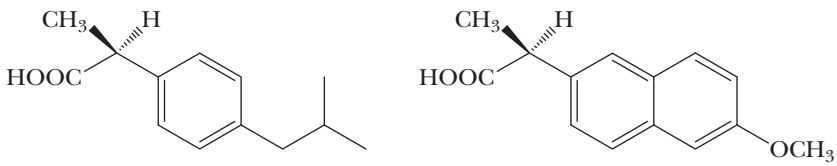


This enantiomer of glyceraldehyde fits the three specific binding sites on the enzyme surface

This enantiomer of glyceraldehyde does not fit the same binding sites

FIGURE 6.7 A schematic diagram of an enzyme surface capable of interacting with (*R*)-(+)-glyceraldehyde at three binding sites, but with (*S*)-(–)-glyceraldehyde at only two of these sites.

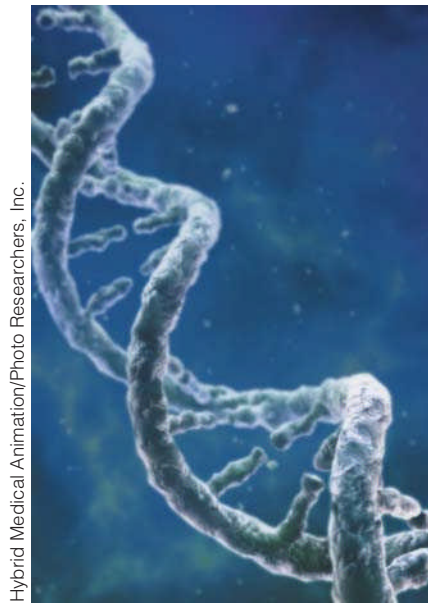
Because interactions between molecules in living systems take place in a chiral environment, it should come as no surprise that a molecule and its enantiomer or one of its diastereomers elicit different physiological responses. As we have already seen, (*S*)-ibuprofen is active as a pain and fever reliever, whereas its R enantiomer is inactive. The S enantiomer of the closely related analgesic naproxen is also the active pain reliever of this compound, but its R enantiomer is a liver toxin!



(*S*)-Ibuprofen (*S*)-Naproxen

6.10 How Can Enantiomers Be Resolved?

Resolution is the separation of a racemic mixture into its enantiomers. Because two enantiomers have the same physical properties, separating them, in general, is difficult, but scientists have developed a number of ways to do it. In this section, we illustrate the use of enzymes as chiral catalysts for separating one enantiomer from another.



Hybrid Medical Animation/Photo Researchers, Inc.

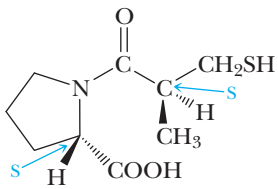
DNA is one example from biology where chiral molecules exist in only one stereoisomeric form.

Resolution Separation of a racemic mixture into its enantiomers.

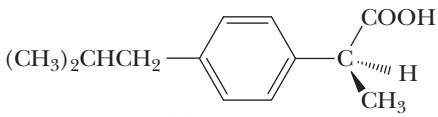
Chemical Connections 6A

CHIRAL DRUGS

Some of the common drugs used in human medicine (for example, aspirin, Section 14.4B) are achiral. Others are chiral and are sold as single enantiomers. The penicillin and erythromycin classes of antibiotics and the drug Captopril are all chiral drugs. Captopril, which is highly effective for the treatment of high blood pressure and congestive heart failure, was developed in a research program designed to discover effective inhibitors of angiotensin-converting enzyme (ACE). Captopril is manufactured and sold as the (*S,S*)-stereoisomer. A large number of chiral drugs, however, are sold as racemic mixtures. The popular analgesic ibuprofen (the active ingredient in Motrin®, Advil®, and many other nonaspirin analgesics) is an example. Only the S enantiomer of the pain reliever ibuprofen is biologically active.

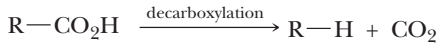


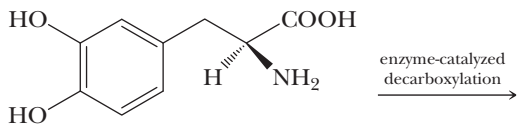
Captopril



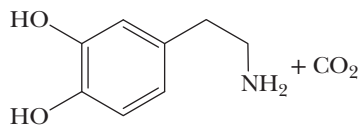
(*S*)-Ibuprofen

For racemic drugs, most often only one enantiomer exerts the beneficial effect, whereas the other enantiomer either has no effect or may exert a detrimental effect. Thus, enantiomerically pure drugs should, more often than not, be more effective than their racemic counterparts. A case in point is 3,4-dihydroxyphenylalanine, which is used in the treatment of Parkinson's disease. The active drug is dopamine. Unfortunately, this compound does not cross the blood–brain barrier to the required site of action in the brain. Consequently, what is administered instead is the prodrug, a compound that is not active by itself, but is converted in the body to an active drug. 3,4-Dihydroxyphenylalanine is such a prodrug; it crosses the blood–brain barrier and then undergoes decarboxylation, catalyzed by the enzyme dopamine decarboxylase, to give dopamine. Decarboxylation is the loss of carbon dioxide from a carboxyl group (R—CO_2H).





(*S*)-(–)-3,4-Dihydroxyphenylalanine
(L-DOPA)
$[\alpha]_D^{13}$ –13.1°

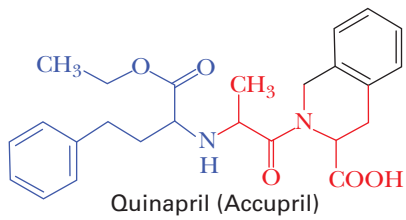


Dopamine

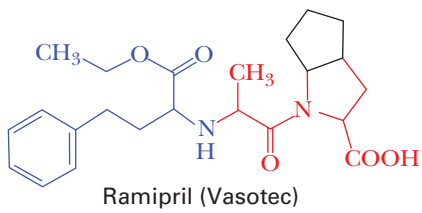
Dopamine decarboxylase is specific for the S enantiomer, which is commonly known as L-DOPA. It is essential, therefore, to administer the enantiomerically pure prodrug. Were the prodrug to be administered in a racemic form, there could be a dangerous buildup of the R enantiomer, which cannot be metabolized by the enzymes present in the brain.

Question

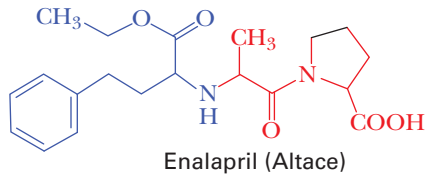
Following are structural formulas for three other angiotensin-converting enzyme (ACE) inhibitors, all members of the *"pril"* family. Which are chiral? For each that is chiral, determine the number of stereoisomers possible for it. List the similarities in structure among each of these four drugs.



Quinapril (Accupril)



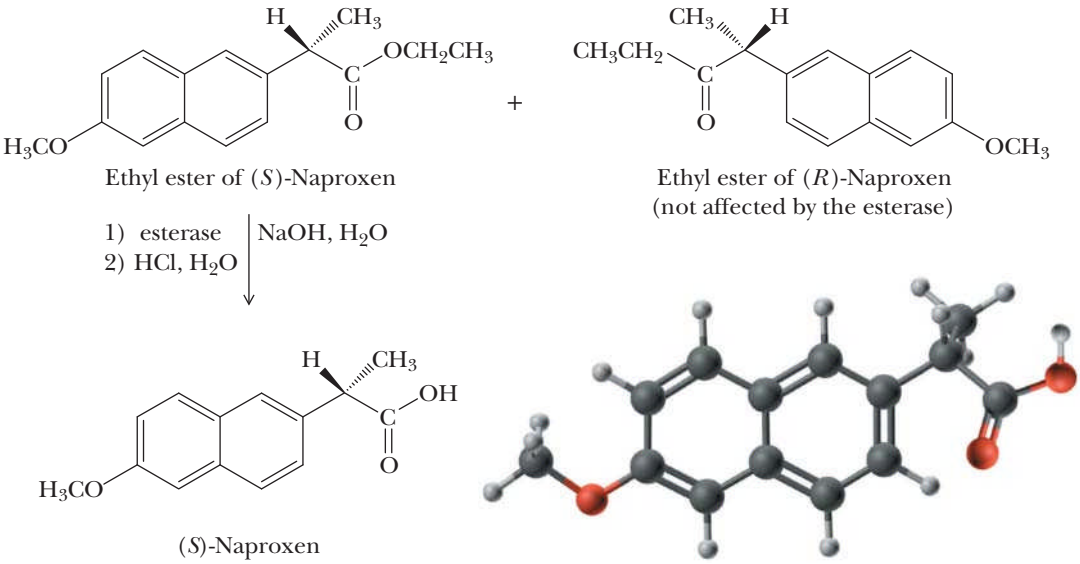
Ramipril (Vasotec)



Enalapril (Altace)

Enzymes as Resolving Agents

One class of enzymes that has received particular attention in this regard is the esterases, which catalyze the hydrolysis of esters (Section 14.1C) to give an alcohol and a carboxylic acid. We illustrate this method by describing the resolution of (*R*,*S*)-naproxen. The ethyl esters of both (*R*)- and (*S*)-naproxen are solids with very low solubilities in water. Chemists then use an esterase in alkaline solution to selectively hydrolyze the (*S*)-ester, which goes into the aqueous solution as the sodium salt of the (*S*)-carboxylic acid. The (*R*)-ester is unaffected by these conditions. Filtering the alkaline solution recovers the crystals of the (*R*)-ester. After the crystals are removed, the alkaline solution is acidified to precipitate pure (*S*)-naproxen. The recovered (*R*)-ester can be racemized (converted to an *R*,*S*-mixture) and again treated with the esterase. Thus, by recycling the (*R*)-ester, all the racemic ester is converted to (*S*)-naproxen.



Ethyl ester of (*S*)-Naproxen

Ethyl ester of (*R*)-Naproxen
(not affected by the esterase)

(*S*)-Naproxen

The sodium salt of (*S*)-naproxen is the active ingredient in Aleve® and a score of other over-the-counter nonsteroidal anti-inflammatory preparations.

Recently, the U.S. Food and Drug Administration established new guidelines for the testing and marketing of chiral drugs. After reviewing these guidelines, many drug companies have decided to develop only single enantiomers of new chiral drugs. In addition to regulatory pressure, there are patent considerations: If a company has patents on a racemic drug, a new patent can often be taken out on one of its enantiomers.

SUMMARY OF KEY QUESTIONS

6.1 What Are Stereoisomers?

- **Stereoisomers** have the same connectivity of their atoms, but a different three-dimensional orientation of their atoms in space.
- A **mirror image** is the reflection of an object in a mirror.

6.2 What Are Enantiomers?

- **Enantiomers** are a pair of stereoisomers that are nonsuperposable mirror images. A molecule that is not superposable on its mirror image is said to be **chiral**.
- Chirality is a property of an object as a whole, not of a particular atom.
- An **achiral** object possesses a **plane of symmetry**—an imaginary plane passing through the object and dividing it such that one half is the reflection of the other half.
- A **stereocenter** is an atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer.
- The most common type of stereocenter among organic compounds is a **chiral center**, a tetrahedral carbon atom with four different groups bonded to it.

6.3 How Do We Designate the Configuration of a Stereocenter?

- The **configuration** at a stereocenter can be specified by the **R,S convention**.
- To apply this convention, (1) each atom or group of atoms bonded to the stereocenter is assigned a priority and numbered from highest priority to lowest priority, (2) the molecule is oriented in space so that the group of lowest priority is directed away from the observer, and (3) the remaining three groups are read in order, from highest priority to lowest priority.
- If the reading of groups is clockwise, the configuration is **R** (Latin: *rectus*, right). If the reading is counterclockwise, the configuration is **S** (Latin: *sinister*, left).

6.4 What Is the 2^n Rule?

- For a molecule with ***n*** stereocenters, the maximum number of stereoisomers possible is $\mathbf{2^n}$.
- **Diastereomers** are stereoisomers that are not mirror images.
- Certain molecules have special symmetry properties that reduce the number of stereoisomers to fewer than that predicted by the $\mathbf{2^n}$ **rule**.
- A **meso** compound contains two or more stereocenters assembled in such a way that its molecules are achiral.
- Enantiomers have identical physical and chemical properties in achiral environments.
- Diastereomers have different physical and chemical properties.

6.5 How Do We Describe the Chirality of Cyclic Molecules with Two Stereocenters?

- When evaluating the symmetry of cyclic structures, such as derivatives of cyclohexane and cyclopentane, it is helpful to evaluate planar representations.

6.6 How Do We Describe the Chirality of Molecules with Three or More Stereocenters?

- For a molecule with *n* stereocenters, the maximum number of stereoisomers possible is 2^n.

6.7 What Are the Properties of Stereoisomers?

- Enantiomers have identical physical and chemical properties in achiral environments.
- Diastereomers have different physical and chemical properties.

6.8 How Is Chirality Detected in the Laboratory?

- Light that vibrates in only parallel planes is said to be **plane polarized**.
- A **polarimeter** is an instrument used to detect and measure the magnitude of optical activity. **Observed rotation** is the number of degrees the plane of polarized light is rotated.
- **Specific rotation** is the observed rotation measured with a cell 1 dm long and a solution with a concentration of 1.00 g/mL.
- If the analyzing filter must be turned clockwise to restore the zero point, the compound is **dextrorotatory**. If the analyzing filter must be turned counterclockwise to restore the zero point, the compound is **levorotatory**.
- A compound is said to be **optically active** if it rotates the plane of polarized light. Each member of a pair of enantiomers rotates the plane of polarized light an equal number of degrees, but opposite in direction.
- A **racemic mixture** is a mixture of equal amounts of two enantiomers and has a specific rotation of zero.
- A **meso** compound is optically inactive.

6.9 What Is the Significance of Chirality in the Biological World?

- An enzyme catalyzes the biological reactions of molecules by first positioning them at a binding site on its surface. An enzyme with a binding site specific for three of the four groups on a stereocenter can distinguish between a molecule and its enantiomer or its diastereomers.

6.10 How Can Enantiomers Be Resolved?

- **Resolution** is the experimental process of separating a mixture of enantiomers into two pure enantiomers.
- One means of resolution is to treat the racemic mixture with an enzyme that catalyzes a specific reaction of one enantiomer, but not the other.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Enantiomers are always chiral. (6.2)
2. An unmarked cube is chiral. (6.1)
3. Stereocenters can be designated using E and Z. (6.3)
4. A chiral molecule will always have a diastereomer. (6.2)
5. Every object in nature has a mirror image. (6.1)
6. A molecule that possesses an internal plane of symmetry can never be chiral. (6.2)
7. Pairs of enantiomers have the same connectivity. (6.1)
8. Enantiomers, like gloves, occur in pairs. (6.2)
9. A cyclic molecule with two stereocenters will always have only three stereoisomers. (6.5)
10. An achiral molecule will always have a diastereomer. (6.2)
11. The *cis* and *trans* isomers of 2-butene are chiral. (6.1)
12. A human foot is chiral. (6.1)

13. A compound with n stereocenters will always have 2^n stereoisomers. (6.4)

14. A molecule with three or more stereocenters cannot be meso. (6.6)

15. A molecule with three or more stereocenters must be chiral. (6.6)

16. Each member of a pair of enantiomers will have the same boiling point. (6.7)

17. If a molecule is not superposable on its mirror image, it is chiral. (6.1)

18. For a molecule with two tetrahedral stereocenters, four stereoisomers are possible. (6.2)

19. Constitutional isomers have the same connectivity. (6.1)

20. Enantiomers can be separated by interacting them with the same chiral environment or chemical agent. (6.10)

21. Enzymes are achiral molecules that can differentiate chiral molecules. (6.9)

22. *Cis* and *trans* stereoisomers of a cyclic compound can be classified as diastereomers. (6.5)

23. 3-Pentanol is the mirror image of 2-pentanol. (6.2)

24. Diastereomers do not have a mirror image. (6.2)

25. The most common cause of chirality in organic molecules is the presence of a tetrahedral carbon atom with four different groups bonded to it. (6.1)

26. Each member of a pair of enantiomers will have the same density. (6.7)

27. The carbonyl carbon of an aldehyde or a ketone cannot be a stereocenter. (6.1)

28. For a molecule with three stereocenters, $3^2 = 9$ stereoisomers are possible. (6.2)

29. Diastereomers can be resolved using traditional methods such as distillation. (6.10)

30. A racemic mixture is optically inactive. (6.8)

31. 2-Pentanol and 3-pentanol are chiral and show enantiomerism. (6.2)

32. A diastereomer of a chiral molecule must also be chiral. (6.2)

33. In order to designate the configuration of a stereocenter, the priority of groups must be read in a clockwise or counterclockwise fashion after the lowest priority group is placed facing toward the viewer. (6.3)

34. A compound with n stereocenters will always be one of the 2^n stereoisomers of that compound. (6.4)

35. Each member of a pair of enantiomers could react differently in a chiral environment. (6.7)

36. A chiral molecule will always have an enantiomer. (6.2)

37. Each member of a pair of diastereomers will have the same melting point. (6.7)

38. If a chiral compound is dextrorotatory, its enantiomer is levorotatory by the same number of degrees. (6.8)

39. All stereoisomers are optically active. (6.8)

40. There are usually equal amounts of each enantiomer of a chiral biological molecule in a living organism. (6.9)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) F (3) F (4) F (5) T (6) T (7) T (8) T (9) F
(10) F (11) F (12) T (13) F (14) F (15) F (16) T (17) T (18) T
(19) F (20) T (21) F (22) T (23) F (24) F (25) T (26) T (27) T
(28) F (29) T (30) T (31) F (32) F (33) F (34) T (35) T (36) T
(37) F (38) T (39) F (40) F

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 6.1 Chirality

6.7 Define the term *stereoisomer*. Name four types of stereoisomers.

6.8 In what way are constitutional isomers different from stereoisomers? In what way are they the same?

6.9 Compare and contrast the meaning of the terms *conformation* and *configuration*.

***6.10** Which of these objects are chiral (assume that there is no label or other identifying mark)?

(a) A pair of scissors
(b) A tennis ball
(c) A paper clip
(d) A beaker
(e) The swirl created in water as it drains out of a sink or bathtub

***6.11** Think about the helical coil of a telephone cord or the spiral binding on a notebook, and suppose that you view the spiral from one end and find that it has a left-handed twist. If you view the same spiral from the other end, does it have a right-handed twist or a left-handed twist from that end as well?

***6.12** Next time you have the opportunity to view a collection of augers or other seashells that have a helical twist, study the chirality of their twists. Do you find an equal number of left-handed and right-handed augers, or, for example, do they all have the same handedness? What about the handedness of augers compared with that of other spiral shells?

Kaz Chiba/Getty Images, Inc.

Median cross section through the shell of a chambered nautilus found in the deep waters of the Pacific Ocean. The shell shows handedness; this cross section is a right-handed spiral.

***6.13** Next time you have an opportunity to examine any of the seemingly endless varieties of spiral pasta (rotini, fusilli, radiatori, tortiglioni), examine their twist. Do the twists of any one kind all have a right-handed twist, do they all have a left-handed twist, or are they a racemic mixture?

6.14 One reason we can be sure that sp^3 hybridized carbon atoms are tetrahedral is the number of stereoisomers that can exist for different organic compounds.

(a) How many stereoisomers are possible for $CHCl_3$, CH_2Cl_2, and CHBrClF if the four bonds to carbon have a tetrahedral geometry?

(b) How many stereoisomers are possible for each of the compounds if the four bonds to the carbon have a square planar geometry?

SECTION 6.2 Enantiomers

6.15 Which compounds contain stereocenters? **(See Example 6.1)**

(a) 2-Chloropentane

(b) 3-Chloropentane

(c) 3-Chloro-1-pentene

(d) 1,2-Dichloropropane

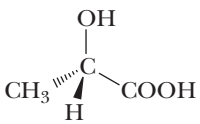
6.16 Using only C, H, and O, write a structural formula for the lowest-molecular-weight chiral molecule of each of the following compounds:

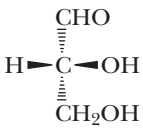
(a) Alkane
(b) Alcohol
(c) Aldehyde
(d) Ketone
(e) Carboxylic acid
(f) Ester

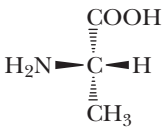
6.17 Which alcohols with the molecular formula $C_5H_{12}O$ are chiral?

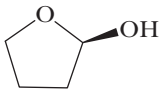
6.18 Which carboxylic acids with the molecular formula $C_6H_{12}O_2$ are chiral?

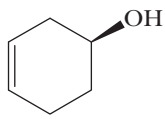
6.19 Draw the enantiomer for each molecule: **(See Example 6.1)**

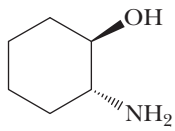
(a) 

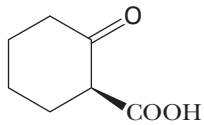
(b) 

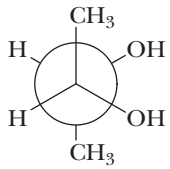
(c) 

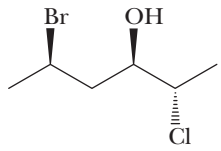
(d) 

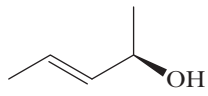
(e) 

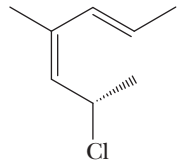
(f) 

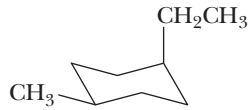
(g) 

(h) 

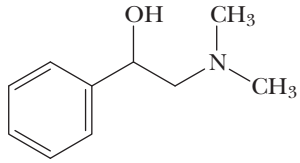
(i) 

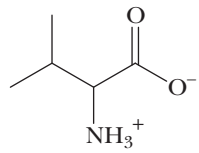
(j) 

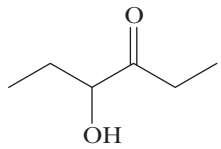
(k) 

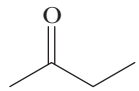
(l) 

6.20 Mark each stereocenter in these molecules with an asterisk (note that not all contain stereocenters): **(See Example 6.1)**

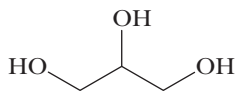
(a) 

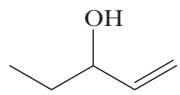
(c) 

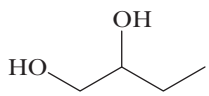
(b) 

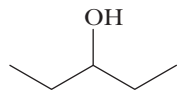
(d) 

6.21 Mark each stereocenter in these molecules with an asterisk (note that not all contain stereocenters): **(See Example 6.1)**

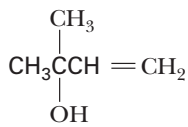
(a) 

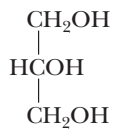
(c) 

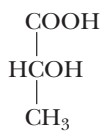
(b) 

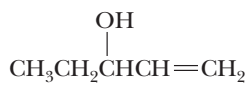
(d) 

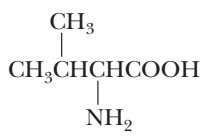
6.22 Mark each stereocenter in these molecules with an asterisk (note that not all contain stereocenters): **(See Example 6.1)**

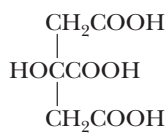
(a) 

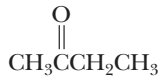
(e) 

(b) 

(f) 

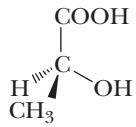
(c) 

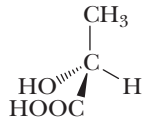
(g) 

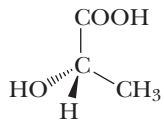
(d) 

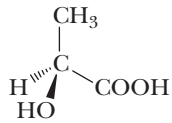
(h) $(CH_3)_3CCH_2CH(OH)CH_3$

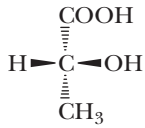
6.23 Following are eight stereorepresentations of lactic acid: **(See Examples 6.3, 6.4)**

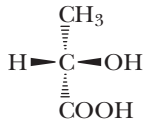
(a) 

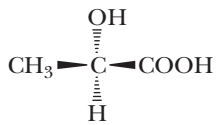
(b) 

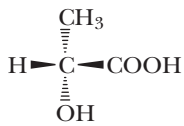
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

Take (a) as a reference structure. Which stereorepresentations are identical with (a) and which are mirror images of (a)?

SECTION 6.3 Designation of Configuration: The R,S Convention

6.24 Assign priorities to the groups in each set: **(See Example 6.2)**

(a) —H —CH_3 —OH —CH_2OH

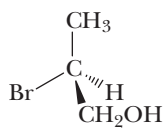
(b) —$CH_2CH{=}CH_2$ —$CH{=}CH_2$ —CH_3 —CH_2COOH

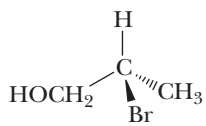
(c) —CH_3 —H —COO^- —NH_3^+

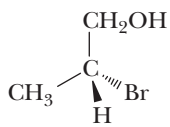
(d) —CH_3 —CH_2SH —NH_3^+ —COO^-

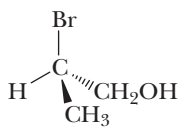
(e) —$CH(CH_3)_2$ —$CH{=}CH_2$ —$C(CH_3)_3$ —C≡CH

6.25 Which molecules have R configurations? **(See Example 6.2)**

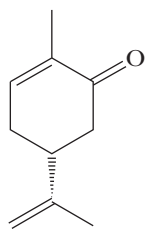
(a) 

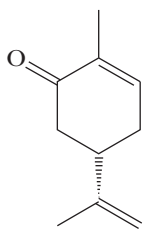
(b) 

(c) 

(d) 

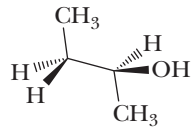
***6.26** Following are structural formulas for the enantiomers of carvone: **(See Example 6.2)**

(–)-Carvone (Spearmint oil) 

 (+)-Carvone (Caraway and dillseed oil)

Each enantiomer has a distinctive odor characteristic of the source from which it can be isolated. Assign an R or S configuration to the stereocenter in each. How can they have such different properties when they are so similar in structure?

6.27 Following is a staggered conformation of one of the stereoisomers of 2-butanol: **(See Example 6.2)**



(a) Is this (*R*)-2-butanol or (*S*)-2-butanol?

(b) Draw a Newman projection for this staggered conformation, viewed along the bond between carbons 2 and 3.

(c) Draw a Newman projection for one more staggered conformations of this molecule. Which of your conformations is the more stable? Assume that —OH and —CH_3 are comparable in size.

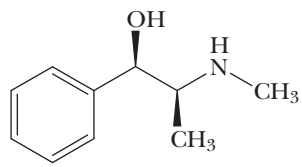
(d) Do diastereomers exist for 2-butanol? If so, draw them.

(e) Is this the dextrorotatory or levorotatory form of 2-butanol?

SECTIONS 6.5 AND 6.6 Molecules with Two or More Stereocenters

6.28 Write the structural formula of an alcohol with molecular formula $C_6H_{14}O$ that contains two stereocenters.

***6.29** For centuries, Chinese herbal medicine has used extracts of *Ephedra sinica* to treat asthma. Investigation of this plant resulted in the isolation of ephedrine, a potent dilator of the air passages of the lungs. The naturally occurring stereoisomer is levorotatory and has the following structure: **(See Example 6.2)**

Ephedrine 

Assign an R or S configuration to each stereocenter.

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Ephedra sinica, a source of ephedrine, a potent bronchodilator.

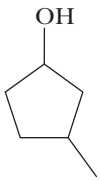
***6.30** The specific rotation of naturally occurring ephedrine, shown in Problem 6.29, is –41°. What is the specific rotation of its enantiomer?

6.31 Label each stereocenter in these molecules with an asterisk and tell how many stereoisomers exist for each. **(See Examples 6.5, 6.6)**

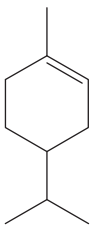
(a) $CH_3CHCHCOOH$ (HO, OH)

(b) $CH_2—COOH$, $CH—COOH$, $HO—CH—COOH$

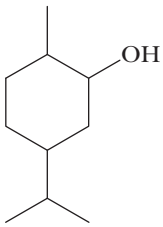
(c)



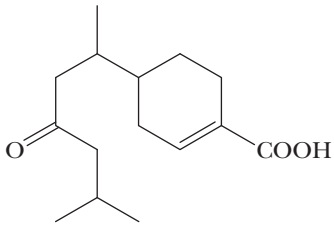
(d)



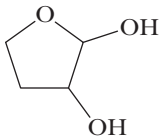
(e)



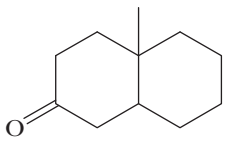
(f)



(g)

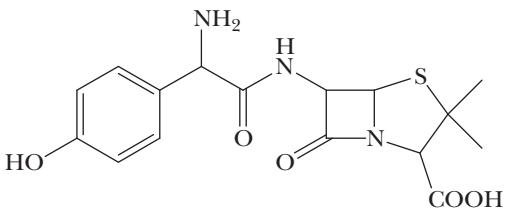


(h)



How many stereoisomers are possible for each compound?

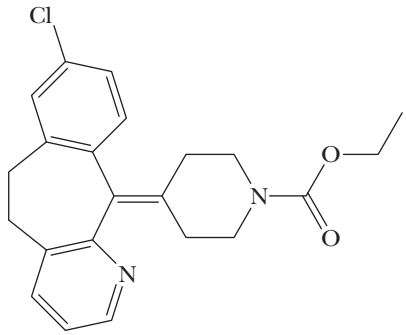
***6.32** Label the four stereocenters in amoxicillin, which belongs to the family of semisynthetic penicillins:



Amoxicillin

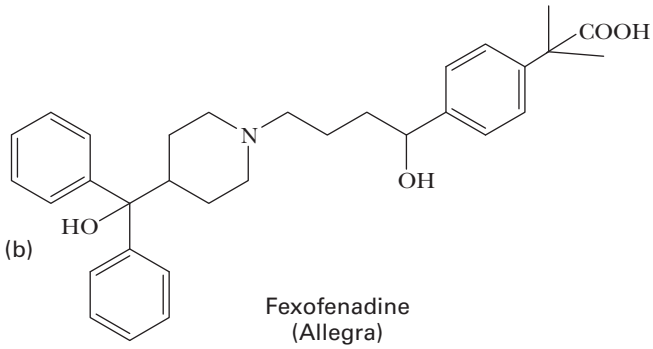
***6.33** Label all stereocenters in loratadine (Claritin®) and fexofenadine (Allegra®), now the top-selling antihistamines in the United States. Tell how many stereoisomers are possible for each. **(See Examples 6.5, 6.6)**

(a)



Loratadine
(Claritin)

(b)

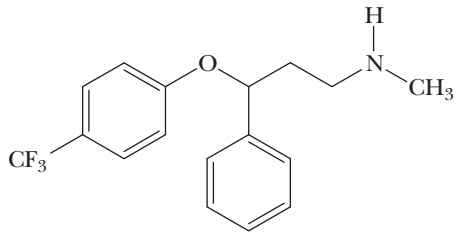


Fexofenadine
(Allegra)

How many stereoisomers are possible for each compound?

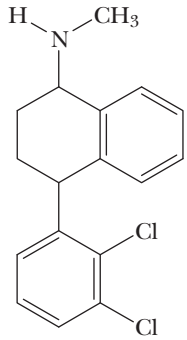
***6.34** Following are structural formulas for three of the most widely prescribed drugs used to treat depression. Label all stereocenters in each compound and tell how many stereoisomers are possible for each compound. **(See Examples 6.5, 6.6)**

(a)



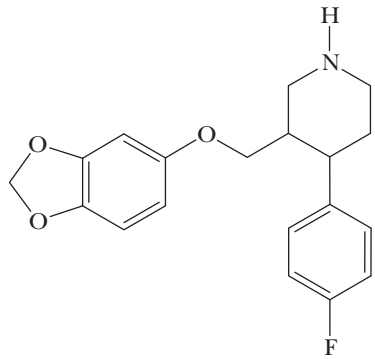
Fluoxetine
(Prozac®)

(b)



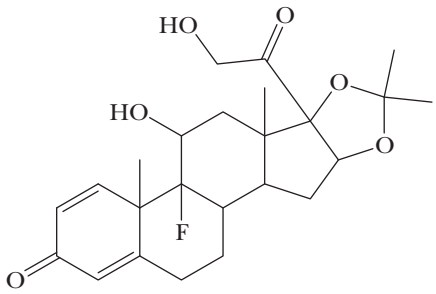
Sertraline
(Zoloft®)

(c)



Paroxetine
(Paxil®)

***6.35** Triamcinolone acetonide, the active ingredient in Azmacort® Inhalation Aerosol, is a steroid used to treat bronchial asthma: **(See Examples 6.5, 6.6)**

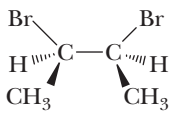


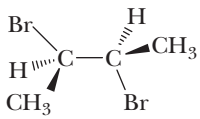
Triamcinolone acetonide

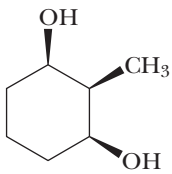
(a) Label the eight stereocenters in this molecule.

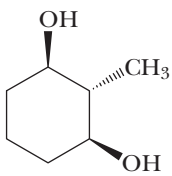
(b) How many stereoisomers are possible for the molecule? (Of this number, only one is the active ingredient in Azmacort.)

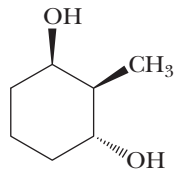
6.36 Which of these structural formulas represent meso compounds? **(See Example 6.4)**

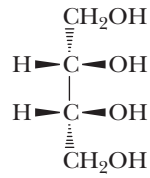
(a) 

(b) 

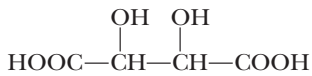
(c) 

(d) 

(e) 

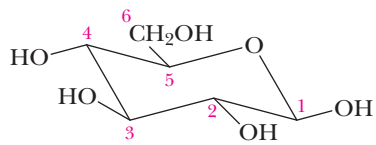
(f) 

6.37 Draw a Newman projection, viewed along the bond between carbons 2 and 3, for both the most stable and the least stable conformations of meso-tartaric acid:



6.38 How many stereoisomers are possible for 1,3-dimethylcyclopentane? Which are pairs of enantiomers? Which are meso compounds? **(See Examples 6.4–6.6)**

6.39 In Problem 3.59, you were asked to draw the more stable chair conformation of glucose, a molecule in which all groups on the six-membered ring are equatorial: **(See Examples 6.2, 6.5, 6.6)**



(a) Identify all stereocenters in this molecule.

(b) How many stereoisomers are possible?

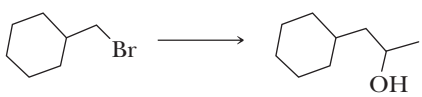
(c) How many pairs of enantiomers are possible?

(d) What is the configuration (*R* or *S*) at carbons 1 and 5 in the stereoisomer shown?

6.40 What is a racemic mixture? Is a racemic mixture optically active? That is, will it rotate the plane of polarized light?

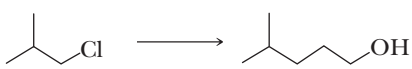
CHEMICAL TRANSFORMATIONS

6.41 Test your cumulative knowledge of the reactions learned so far by completing the following chemical transformations. Pay particular attention to the stereochemistry in the product. Where more than one stereoisomer is possible, show each stereoisomer. *Note that some transformations will require more than one step.*

(a) 

(b) 

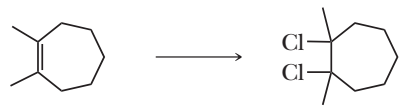
(c) 

(d) 

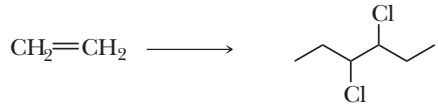
(e) 

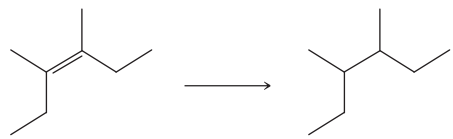
(f) 

(g) 

(h) 

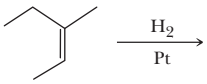
(i) 

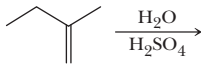
(j) 

(k) 

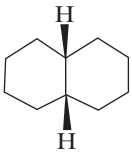
LOOKING AHEAD

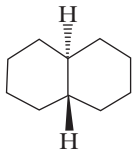
6.42 Predict the product(s) of the following reactions (in cases where more than one stereoisomer is possible, show each stereoisomer):

(a) 

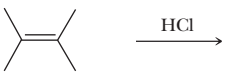
(b) 

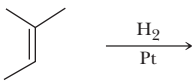
6.43 What alkene, when treated with H_2/Pd, will ensure a 100% yield of the stereoisomer shown?

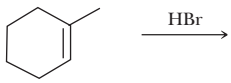
(a) 

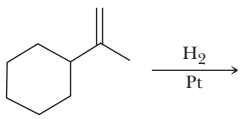
(b) 

6.44 Which of the following reactions will yield a racemic mixture of products?

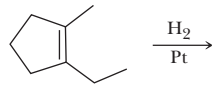
(a) 

(b) 

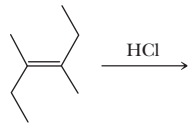
(c) 

(d) 

(e) 

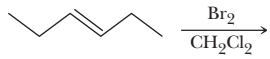
(f) 

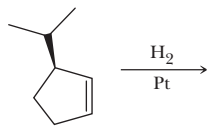
6.45 Draw all the stereoisomers that can be formed in the following reaction:



Comment on the utility of this particular reaction as a synthetic method.

6.46 Explain why the product of the following reaction does not rotate the plane of polarized light:

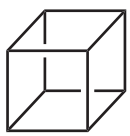
(a) 

(b) 

GROUP LEARNING ACTIVITIES

6.47 Identify objects in your surroundings and take turns deciding if each object is chiral or achiral.

6.48 Take turns identifying the planes of symmetry in cubane (note: the hydrogen atoms are not shown).



Cubane

6.49 Discuss whether the following pairs of objects are true enantiomers of each other. For those that are not true enantiomers, decide what it would take for them to be true enantiomers.

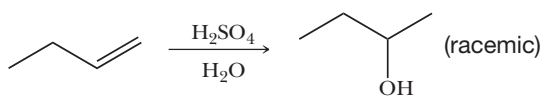
(a) your right hand and left hand

(b) your right eye and left eye

(c) a car with a left, front flat tire and the same car with a right, front flat tire

6.50 Compound **A** (C_5H_8) is not optically active and cannot be resolved. It reacts with Br_2 in CCl_4 to give compound **B** ($C_5H_8Br_2$). When compound **A** is treated with H_2/Pt, it is converted to compound **C** (C_5H_{10}). When treated with HBr, compound **A** is converted to compound **D** (C_5H_9Br). Given this information, propose structural formulas for **A**, **B**, **C**, and **D**. There are at least three possibilities for compound **A** and, in turn, three possibilities for compounds **B**, **C**, and **D**. As a group, try to come up with all the possibilities.

6.51 In Section 5.2, we learned that a reaction mechanism must be consistent with all experimental observations, and in Section 5.3 we proposed a mechanism for the acid-catalyzed hydration of 1-butene to give 2-butanol. In this chapter, we learned that 2-butanol is chiral, with a maximum of two stereoisomers (a pair of enantiomers) possible. Experimentally, the acid-catalyzed hydration of 1-butene gives a racemic mixture of (*R*)-2-butanol and (*S*)-2-butanol. Show, using illustrations, that the formation of a racemic product is consistent with the mechanism proposed in Section 5.3.



1-Butene 2-Butanol

PUTTING IT TOGETHER

The following problems bring together concepts and material from Chapters 4–6. Although the focus may be on these chapters, the problems will also build on concepts discussed thus far.

Choose the best answer for each of the following questions.

1. Which of the following will *not* rotate the plane of polarized light?

(a) A 50:50 ratio of (*R*)-2-butanol and *cis*-2-butene.

(b) A 70:20 ratio of (*R*)-2-butanol and *S*-2-butanol.

(c) A 50:25:25 ratio of (*S*)-2-butanol, *cis*-2-butene, and *trans*-2-butene.

(d) A 20:70 ratio of *trans*-2-butene and *cis*-2-butene.

(e) None of the above (i.e., all of them will rotate plane-polarized light)

2. Which of the following *cis* isomers of dimethylcyclohexane is *not* meso?

(a) *cis*-1,4-dimethylcyclohexane

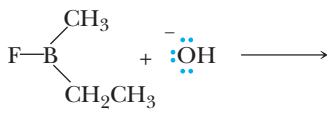
(b) *cis*-1,3-dimethylcyclohexane

(c) *cis*-1,2-dimethylcyclohexane

(d) All of the above (i.e., none of them is meso)

(e) None of the above (i.e., all of them are meso)

3. How many products are possible in the following Lewis acid–base reaction?



(a) One

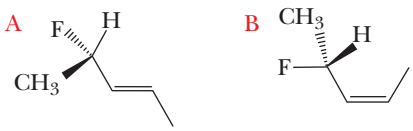
(b) Two

(c) Three

(d) Four

(e) None (no reaction will take place)

4. What is the relationship between the following two molecules?



(a) They are identical.

(b) They are enantiomers.

(c) They are diastereomers.

(d) They are constitutional isomers.

(e) They are nonisomers.

5. Which stereoisomer of 2,4-hexadiene is the *least* stable?

(a) *Z,Z*-2,4-hexadiene

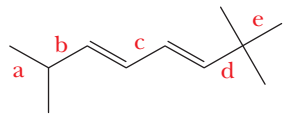
(b) *Z,E*-2,4-hexadiene

(c) *E,Z*-2,4-hexadiene

(d) *E,E*-2,4-hexadiene

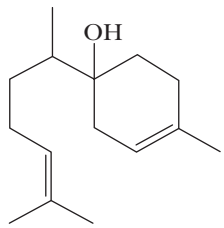
(e) All are equal in stability.

6. Select the shortest C—C single bond in the following molecule.



(a) a (b) b (c) c (d) d (e) e

7. Which of the following statements is true of β-bisabolol?



β-Bisabolol

(a) There are 6 stereoisomers of β-bisabolol.

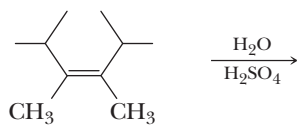
(b) β-Bisabolol is soluble in water.

(c) β-Bisabolol is achiral.

(d) β-Bisabolol has a meso stereoisomer.

(e) None of the above.

8. How many products are formed in the following reaction?



(a) 1 (b) 2 (c) 3 (d) 4 (e) 5

9. Which of the following is *true* when two isomeric alkenes are treated with H_2/Pt?

(a) The alkene that releases more energy in the reaction is the more stable alkene.

(b) The alkene with the lower melting point will release less energy in the reaction.

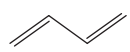
(c) The alkene with the lower boiling point will release less energy in the reaction.

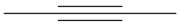
(d) Both alkenes will release equal amounts of energy in the reaction.

(e) None of these statements is true.

10. An unknown compound reacts with two equivalents of H_2 catalyzed by Ni. The unknown also yields 5 CO_2 and 4 H_2O upon combustion. Which of the following could be the unknown compound?

(a) 

(b) 

(c) 

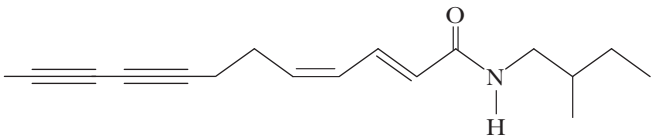
(d) 

(e) 

(f) $CH_3CH=CHCH_2CH_3$

11. Provide structures for all possible compounds of formula C_5H_6 that would react quantitatively with $NaNH_2$.

12. Answer the questions that follow regarding the following compound, which has been found in herbal preparations of *Echinacea*, the genus name for a variety of plants marketed for their immunostimulant properties.



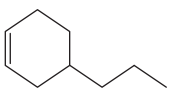
(a) How many stereoisomers exist for the compound shown?

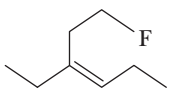
(b) Would you expect the compound to be soluble in water?

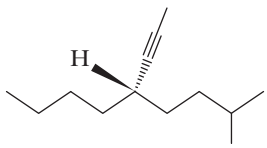
(c) Is the molecule chiral?

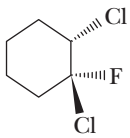
(d) What would be the product formed in the reaction of this compound with an excess amount of H_2/Pt?

13. Provide IUPAC names for the following compounds.

(a) 

(b) 

(c) 

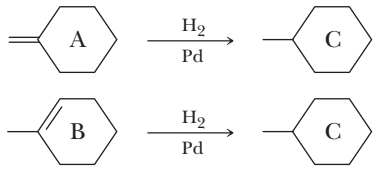
(d) 

14. Compound **A** is an optically inactive compound with a molecular formula of C_5H_8. Catalytic hydrogenation of **A** gives an optically inactive compound, **B** (C_5H_{10}), as the sole product. Furthermore, reaction of **A** with HBr results in a single compound, **C**, with a molecular formula of C_5H_9Br. Provide structures for **A**, **B**, and **C**.

15. An optically active compound, **A**, has a molecular formula of C_6H_{12}. Hydroboration–oxidation of **A** yields an optically active product, **B**, with a molecular formula of $C_6H_{14}O$. Catalytic hydrogenation of **A** yields an optically inactive product, **C**, with a molecular formula of C_6H_{14}. Propose structures for **A**, **B**, and **C**.

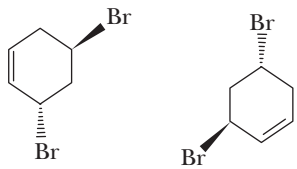
16. Based on the following hydrogenation data, which is more stable, the alkene **(A)** with the double bond outside of the ring or the alkene **(B)** with the double bond inside the ring? Use a reaction energy diagram to illustrate your point.

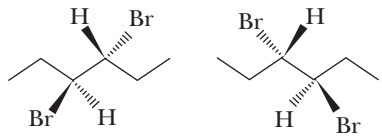
$\Delta H = -23.84$ kcal/mol

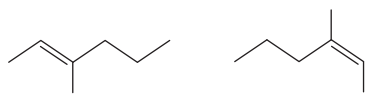


$\Delta H = -20.69$ kcal/mol

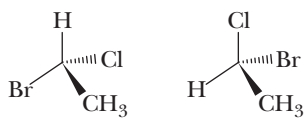
17. Explain whether the following pairs of compounds could be separated by resolution of enantiomers. If such separation is not possible, indicate so and explain your answer.

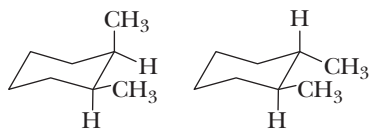
(a) 

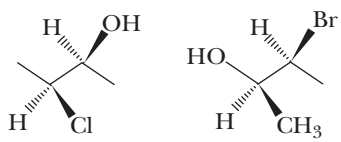
(b) 

(c) 

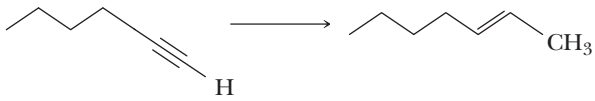
18. Predict whether solutions containing equal amounts of each pair of the structures shown would rotate the plane of polarized light.

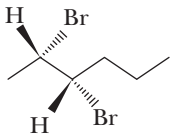
(a) 

(b) 

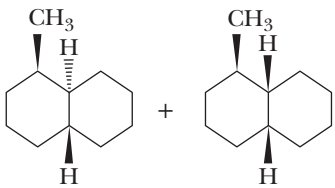
(c) 

19. Complete the following chemical transformations.

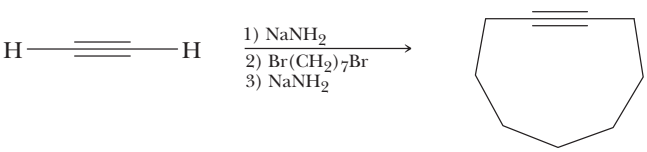
(a) 

(b) Any alkyne ⟶ 

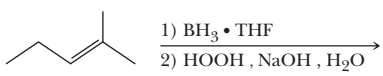
+ enantiomer

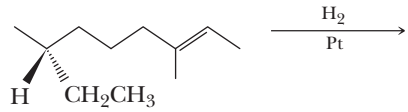
(c) Any alkene ⟶ 

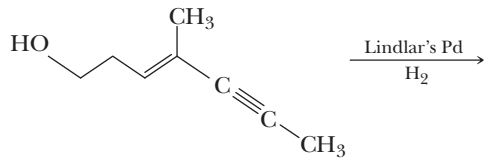
20. Provide a mechanism for the following series of reactions. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.



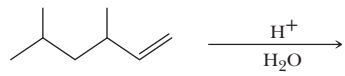
21. Predict the major product or products of each of the following reactions. Be sure to consider stereochemistry in your answers.

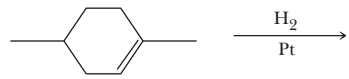
(a) 

(b) 

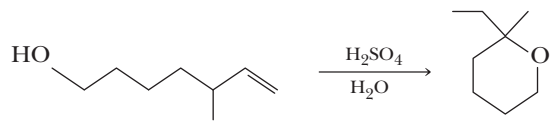
(c) 

(d) 

(e) 

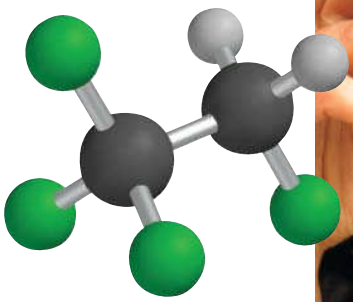
(f) 

22. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.



Haloalkanes

7



Asthma patient using a metered-dose inhaler to deliver the drug albuterol. The drug is propelled by haloalkanes such as 1,1,1,2-tetrafluoroethane. Inset: A molecule of 1,1,1,2-tetrafluoroethane (HFA-134a).

Carolyn A. McKeone/Photo Researchers, Inc.

Haloalkane (alkyl halide)
A compound containing a halogen atom covalently bonded to an sp^3 hybridized carbon atom; given the symbol RX.

YOU MAY HAVE HEARD of the term chlorofluorocarbons and their well-documented harm to the environment. Chlorofluorocarbons belong to a larger class of compounds named **haloalkanes** or, in the common system of nomenclature, *alkyl halides*, compounds containing at least one halogen atom covalently bonded to an sp^3 hybridized carbon atom. The general symbol for an **alkyl halide** is R—X, where X may be F, Cl, Br, or I:

A haloalkane (An alkyl halide)

In this chapter, we study two characteristic reactions of haloalkanes: nucleophilic substitution and β-elimination. We will see that haloalkanes can be quite useful molecules because they can be converted to alcohols, ethers, thiols, amines, and alkenes and are

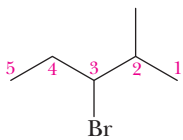
thus versatile molecules. Indeed, haloalkanes are often used as starting materials for the synthesis of many useful compounds encountered in medicine, food chemistry, and agriculture (to name a few).

7.1 How Are Haloalkanes Named?

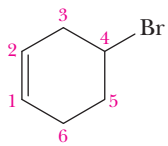
A. IUPAC Names

IUPAC names for haloalkanes are derived by naming the parent alkane according to the rules given in Section 3.3A:

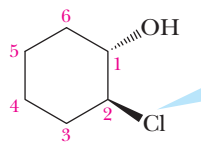
- Locate and number the parent chain from the direction that gives the substituent encountered first the lower number.
- Show halogen substituents by the prefixes *fluoro-*, *chloro-*, *bromo-*, and *iodo-*, and list them in alphabetical order along with other substituents.
- Use a number preceding the name of the halogen to locate each halogen on the parent chain.
- In haloalkenes, the location of the double bond determines the numbering of the parent hydrocarbon. In molecules containing functional groups designated by a suffix (for example, *-ol*, *-al*, *-one*, *-oic acid*), the location of the functional group indicated by the suffix determines the numbering:



3-Bromo-2-methylpentane



4-Bromocyclohexene

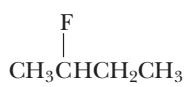


(1*S*,2*S*)-2-Chlorocyclohexanol
or
trans-2-Chlorocyclohexanol

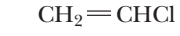
haloalkanes are named by treating the halogen as substituents in the IUPAC system of nomenclature

B. Common Names

Common names of haloalkanes consist of the common name of the alkyl group, followed by the name of the halide as a separate word. Hence, the name alkyl halide is a common name for this class of compounds. In the following examples, the IUPAC name of the compound is given first, followed by its common name, in parentheses:



2-Fluorobutane
(*sec*-Butyl fluoride)



Chloroethene
(Vinyl chloride)

Several of the polyhalomethanes are common solvents and are generally referred to by their common, or trivial, names. Dichloromethane (methylene chloride) is the most widely used haloalkane solvent. Compounds of the type CHX_3 are called **haloforms**. The common name for $CHCl_3$, for example, is *chloroform*. The common name for CH_3CCl_3 is *methyl chloroform*. Methyl chloroform and trichloroethylene are solvents for commercial dry cleaning.

© moodboard/Alamy Inc

Tetrachloroethylene, $Cl_2C{=}CCl_2$, is commonly used as a dry cleaning solvant.

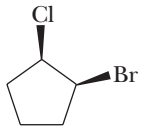
CH_2Cl_2	$CHCl_3$	CH_3CCl_3	$Cl_2C=CCl_2$
Dichloromethane	Trichloromethane	1,1,1-Trichloroethane	Tetrachloroethene
(Methylene chloride)	(Chloroform)	(Methyl chloroform)	(Tetrachloroethylene)

Name Cyclic Haloalkanes

HOW TO 7.1

(a) First, determine the root name of the cycloalkane.

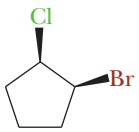
the root name of a 5-carbon ring is "cyclopentane"



Cyclopentane

(b) Name and number the halogen substituents.

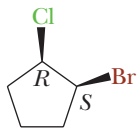
in rings, multiple halogens are listed alphabetically and numbered in alphabetical order



1-Bromo-2-chlorocyclopentane

(c) Don't forget to indicate stereochemistry.

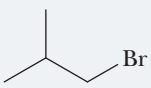
see Chapter 6 for rules on assigning R/S configurations

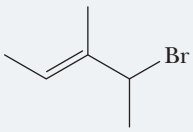


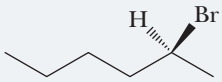
(1*S*,2*R*)-1-Bromo-2-chlorocyclopentane
or
cis -1-Bromo-2-chlorocyclopentane

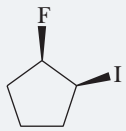
EXAMPLE 7.1

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

(d) 

STRATEGY

First look for the longest chain of carbons. This will allow you to determine the root name. Then identify the atoms or groups of atoms that are not part of that chain of carbons. These are your substituents. Remember to include stereochemical configurations, *E*/*Z* or *R*/*S*, where applicable.

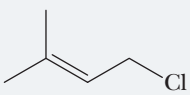
SOLUTION

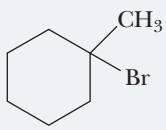
(a) 1-Bromo-2-methylpropane. Its common name is isobutyl bromide.
(b) (*E*)-4-Bromo-3-methyl-2-pentene.
(c) (*S*)-2-Bromohexane.
(d) (1*R*,2*S*)-1-Fluoro-2-iodocyclopentane or *cis*-1-fluoro-2-iodocyclopentane.

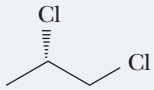
See problems 7.9–7.12

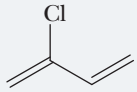
PROBLEM 7.1

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

(d) 

(e) 

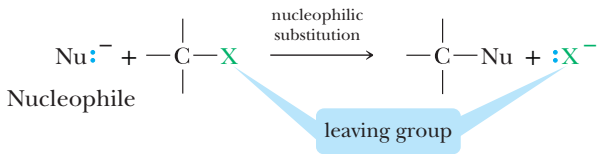
As previously discussed, the **chlorofluorocarbons (CFCs)** manufactured under the trade name Freon® are the most widely known. CFCs are nontoxic, nonflammable, odorless, and noncorrosive. Originally, they seemed to be ideal replacements for the hazardous

compounds such as ammonia and sulfur dioxide formerly used as heat-transfer agents in refrigeration systems. Among the CFCs most widely used for this purpose were trichlorofluoromethane (CCl_3F, Freon-11) and dichlorodifluoromethane (CCl_2F_2, Freon-12). The CFCs also found wide use as industrial cleaning solvents to prepare surfaces for coatings, to remove cutting oils and waxes from millings, and to remove protective coatings. In addition, they were employed as propellants in aerosol sprays. They are now, however, banned from use in most developed countries and replaced with hydrofluorocarbons (see Chemical Connections 7A).

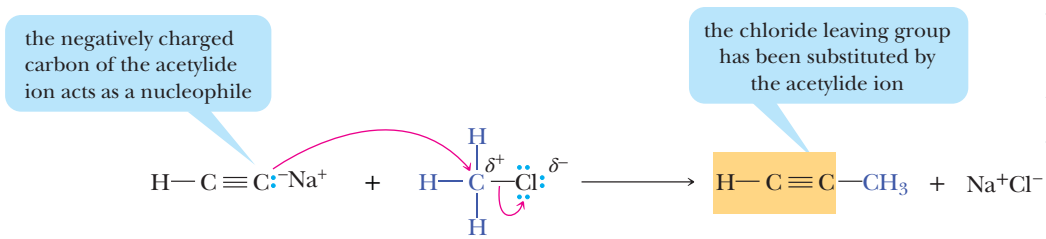
R-410A is a refrigerant that does not contribute to ozone depletion. It consists of a mixture of CH_2F_2 and CHF_2CF_3.

7.2 What Are the Characteristic Reactions of Haloalkanes?

A **nucleophile** (nucleus-loving reagent) is any reagent that donates an unshared pair of electrons to form a new covalent bond. **Nucleophilic substitution** is any reaction in which one nucleophile is substituted for another. In the following general equations, $Nu:^-$ is the nucleophile, X is the leaving group, and substitution takes place on an sp^3 hybridized carbon atom:



Halide ions are among the best and most important leaving groups. Recall from Section 5.7 that nucleophilic substitution occurs in the alkylation of an acetylide ion:



Nucleophile An atom or a group of atoms that donates a pair of electrons to another atom or group of atoms to form a new covalent bond.

Nucleophilic substitution A reaction in which one nucleophile is substituted for another.

Chemical Connections 7A

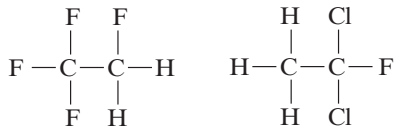
THE ENVIRONMENTAL IMPACT OF CHLOROFLUOROCARBONS

Concern about the environmental impact of CFCs arose in the 1970s when researchers found that more than 4.5×10^5 kg/yr of these compounds were being emitted into the atmosphere. In 1974, Sherwood Rowland and Mario Molina announced their theory, which has since been amply confirmed, that CFCs catalyze the destruction of the stratospheric ozone layer. When released into the air, CFCs escape to the lower atmosphere. Because of their inertness, however, they do not decompose there. Slowly, they find their way to the stratosphere, where they absorb ultraviolet radiation from the sun and then decompose. As they do so, they set up a chemical reaction that leads to the destruction of the stratospheric ozone layer, which shields the Earth against short-wavelength ultraviolet radiation from the sun. An increase in short-wavelength ultraviolet radiation reaching the Earth is believed to promote the destruction of certain crops and agricultural species and even to increase the incidence of skin cancer in light-skinned individuals.

The concern about CFCs prompted two conventions, one in Vienna in 1985 and one in Montreal in 1987, held by the United Nations Environmental Program. The 1987 meeting produced the Montreal Protocol, which set limits on the production and use of ozone-depleting CFCs and urged the complete phase-out of their production by the year 1996. Only two members of the UN have failed to ratify the protocol in its original form.

Rowland, Molina, and Paul Crutzen (a Dutch chemist at the Max Planck Institute for Chemistry in Germany) were awarded the 1995 Nobel Prize for chemistry. As the Royal Swedish Academy of Sciences noted in awarding the prize, "By explaining the chemical mechanisms that affect the thickness of the ozone layer, these three researchers have contributed to our salvation from a global environmental problem that could have catastrophic consequences."

The chemical industry responded to the crisis by developing replacement refrigerants that have a much lower ozone-depleting potential. The most prominent replacements are the hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs), such as the following:



HFC-134a HCFC-141b

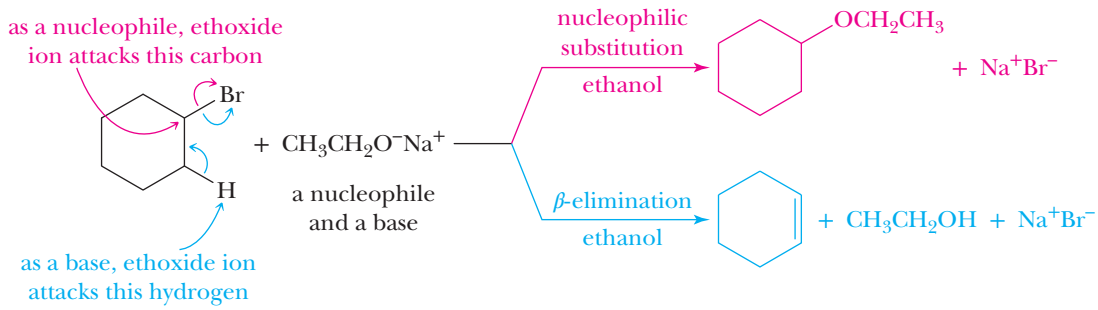
These compounds are much more chemically reactive in the atmosphere than the Freons are and are destroyed before they reach the stratosphere. However, they cannot be used in air conditioners manufactured before 1994 and earlier model cars.

Question

Provide IUPAC names for HFC-134a and HCFC-141b.

***β*-elimination** The removal of atoms or groups of atoms from two adjacent carbon atoms, as for example, the removal of H and X from an alkyl halide or H and OH from an alcohol to form a carbon–carbon double bond.

Because all nucleophiles are also bases, nucleophilic substitution and base-promoted ***β*-elimination** are competing reactions. The ethoxide ion, for example, is both a nucleophile and a base. With bromocyclohexane, it reacts as a nucleophile (pathway shown in red) to give ethoxycyclohexane (cyclohexyl ethyl ether) and as a base (pathway shown in blue) to give cyclohexene and ethanol:



HOW TO 7.2

Recognize Substitution and *β*-Elimination Reactions

(a) Substitution reactions always result in the replacement of one atom or group of atoms in a reactant with another atom or group of atoms.

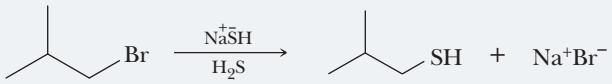
(b) *β*-Elimination reactions always result in the removal of a hydrogen and an atom or group of atoms on adjacent carbon atoms and in the formation of a C—C double bond.

In this chapter, we study both of these organic reactions. Using them, we can convert haloalkanes to compounds with other functional groups including alcohols, ethers, thiols, sulfides, amines, nitriles, alkenes, and alkynes. Thus, an understanding of nucleophilic substitution and *β*-elimination opens entirely new areas of organic chemistry.

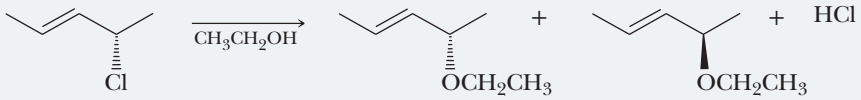
EXAMPLE 7.2

Determine whether the following haloalkanes underwent substitution, elimination, or both substitution and elimination:

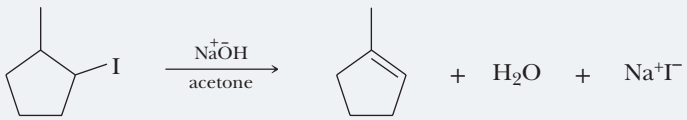
(a)



(b)



(c)



STRATEGY

Look for the halogen in the reactant. Has it been replaced by a different atom or group of atoms in the product(s)? If so, the reaction was a substitution reaction. If the carbon that was once bonded to the halogen is now part of a C—C double bond in the product(s), an elimination reaction has occurred.

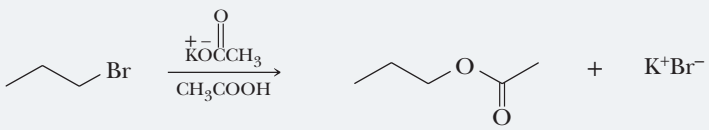
SOLUTION

(a) Substitution; the bromine was replaced by a thiol group.
(b) Substitution; in both products, an ethoxyl group replaces chlorine.
(c) β-Elimination; a hydrogen atom and an iodo group have been removed, and an alkene forms as a result.

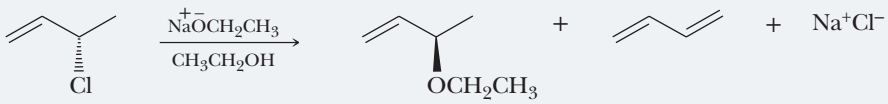
PROBLEM 7.2

Determine whether the following haloalkanes underwent substitution, elimination, or both substitution and elimination:

(a)



(b)



7.3 What Are the Products of Nucleophilic Aliphatic Substitution Reactions?

Nucleophilic substitution is one of the most important reactions of haloalkanes and can lead to a wide variety of new functional groups, several of which are illustrated in Table 7.1. As you study the entries in this table, note the following points:

1. If the nucleophile is negatively charged, as, for example, OH^- and RS^-, then the atom donating the pair of electrons in the substitution reaction becomes neutral in the product.

2. If the nucleophile is uncharged, as, for example, NH_3 and CH_3OH, then the atom donating the pair of electrons in the substitution reaction becomes positively charged in the product. The products then often undergo a second step involving proton transfer to yield a neutral substitution product.

TABLE 7.1 Some Nucleophilic Substitution Reactions

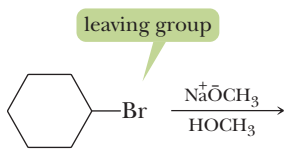
Reaction: $Nu:^- + CH_3X \longrightarrow CH_3Nu + :X^-$

Nucleophile		Product	Class of Compound Formed
$HO:^-$	$\longrightarrow$	CH_3OH	An alcohol
$RO:^-$	$\longrightarrow$	CH_3OR	An ether
$HS:^-$	$\longrightarrow$	CH_3SH	A thiol (a mercaptan)
$RS:^-$	$\longrightarrow$	CH_3SR	A sulfide (a thioether)
$:I:^-$	$\longrightarrow$	$CH_3I:$	An alkyl iodide
$:NH_3$	$\longrightarrow$	$CH_3NH_3^+$	An alkylammonium ion
HOH	$\longrightarrow$	$CH_3\overset{+}{O}(H)H$	An alcohol (after proton transfer)
CH_3OH	$\longrightarrow$	$CH_3\overset{+}{O}(H)CH_3$	An ether (after proton transfer)

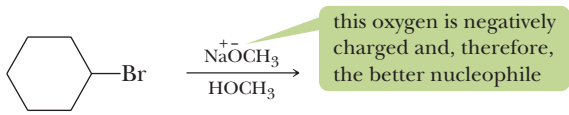
notice that a nucleophile does not need to be negatively charged

HOW TO 7.3 Complete a Substitution Reaction

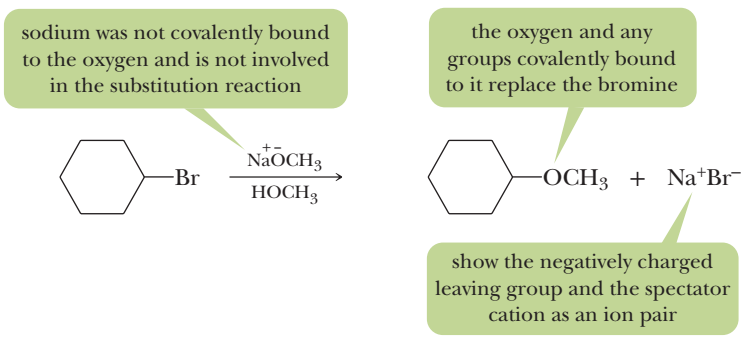
(a) Identify the leaving group.



(b) Identify the nucleophile and its nucleophilic atom. The nucleophilic atom will be the negatively charged atom or the atom with a lone pair of electrons to donate. If both a negatively charged atom and an uncharged atom with a lone pair of electrons exist, the negatively charged atom will be the more nucleophilic atom. In the following example, CH_3O^- is a better nucleophile than $HOCH_3$.

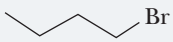
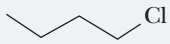


(c) Replace the leaving group in the reactant with the nucleophilic atom or group. Any groups connected to the nucleophilic atom through covalent bonds will remain bonded to that atom in the product. Spectator ions will usually be shown as part of an ion pair with the negatively charged leaving group.



EXAMPLE 7.3

Complete these nucleophilic substitution reactions:

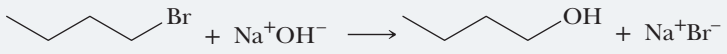
(a)  + Na^+OH^- ⟶ **(b)**  + NH_3 ⟶

STRATEGY

First identify the nucleophile. Then break the bond between the halogen and the carbon it is bonded to and create a new bond from that same carbon to the nucleophile.

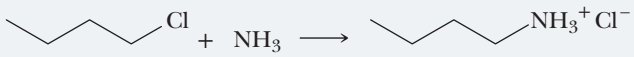
SOLUTION

(a) Hydroxide ion is the nucleophile, and bromine is the leaving group:



1-Bromobutane + Sodium hydroxide ⟶ 1-Butanol + Sodium bromide

(b) Ammonia is the nucleophile, and chlorine is the leaving group:

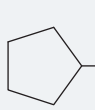


1-Chlorobutane + Ammonia ⟶ Butylammonium chloride

See problems 7.21, 7.22, 7.26

PROBLEM 7.3

Complete these nucleophilic substitution reactions:

(a)  + $CH_3CH_2S^-Na^+$ ⟶ **(b)**  + $CH_3CO^-Na^+$ ⟶

7.4 What Are the S_N2 and S_N1 Mechanisms for Nucleophilic Substitution?

On the basis of a wealth of experimental observations developed over a 70-year period, chemists have proposed two limiting mechanisms for nucleophilic substitutions. A fundamental difference between them is the timing of bond breaking between carbon and the leaving group and of bond forming between carbon and the nucleophile.

A. S_N2 Mechanism

Two processes occur in the S_N2 mechanism: (1) the reaction of an electrophile and a nucleophile to form a new covalent bond and (2) the breaking of a bond to form a stable ion or molecule. At one extreme, the two processes are *concerted*, meaning that bond breaking and bond forming occur simultaneously. Thus, the departure of the leaving group is assisted by the incoming nucleophile. This mechanism is designated **S_N2**, where *S* stands for *S*ubstitution, *N* for *N*ucleophilic, and 2 for a ***bi*molecular reaction**. This type of substitution reaction is classified as bimolecular because both the haloalkane and the nucleophile are involved in the rate-determining step. That is, both species contribute to the rate law of the reaction:

k is the rate constant for the reaction

$$\text{Rate} = k[\text{haloalkane}][\text{nucleophile}]$$

Bimolecular reaction A reaction in which two species are involved in the reaction leading to the transition state of the rate-determining step.

Following is an S_N2 mechanism for the reaction of hydroxide ion and bromomethane to form methanol and bromide ion:

Mechanism

An S_N2 Reaction

The nucleophile attacks the reactive center from the side opposite the leaving group; that is, an S_N2 reaction involves a backside attack by the nucleophile. **(1) The reaction of an electrophile and a nucleophile to form a new covalent bond and (2) the breaking of a bond to form a stable ion or molecule** occur simultaneously.

Inversion of configuration The reversal of the arrangement of atoms or groups of atoms about a reaction center in an S_N2 reaction.

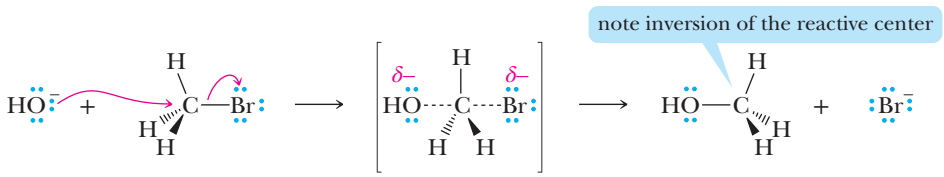


Figure 7.1 shows an energy diagram for an S_N2 reaction. There is a single transition state and no reactive intermediate, and the mechanism takes place in one step.

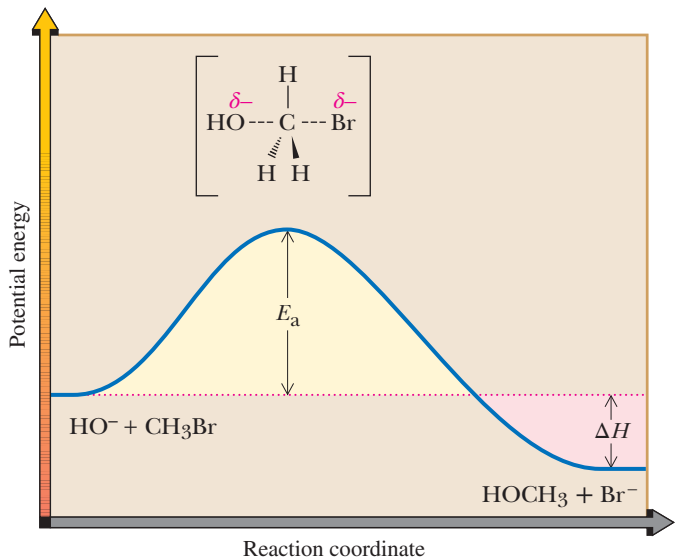
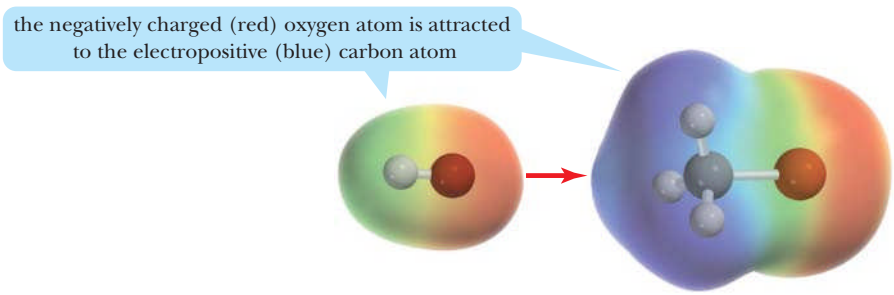


FIGURE 7.1 An energy diagram for an S_N2 reaction. There is one transition state and no reactive intermediate.



Nucleophilic attack from the side opposite the leaving group

An S_N2 reaction is driven by the attraction between the negative charge of the nucleophile (in this case the negatively charged oxygen of the hydroxide ion) and the center of positive charge of the electrophile (in this case the partial positive charge on the carbon bearing the bromine leaving group).

B. S_N1 Mechanism

In the other limiting mechanism, called S_N1, bond breaking between carbon and the leaving group is completed before bond forming with the nucleophile begins. In the designation **S_N1**, *S* stands for *S*ubstitution, *N* stands for *N*ucleophilic, and *1* stands for a ***uni*molecular reaction**. This type of substitution is classified as unimolecular because only the haloalkane is involved in the rate-determining step; that is, only the haloalkane contributes to the rate law governing the rate-determining step:

$$\text{Rate} = k[\text{haloalkane}]$$

Unimolecular reaction A reaction in which only one species is involved in the reaction leading to the transition state of the rate-determining step.

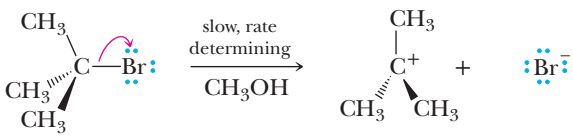
An S_N1 reaction is illustrated by the **solvolysis** reaction of 2-bromo-2-methylpropane (*tert*-butyl bromide) in methanol to form 2-methoxy-2-methylpropane (*tert*-butyl methyl ether). You may notice that the second step of the mechanism is identical to the second step of the mechanism for the addition of hydrogen halides (H—X) to alkenes (Section 5.3A) and the acid-catalyzed hydration of alkenes (Section 5.3B).

Solvolysis A nucleophilic substitution reaction in which the solvent is the nucleophile.

Mechanism

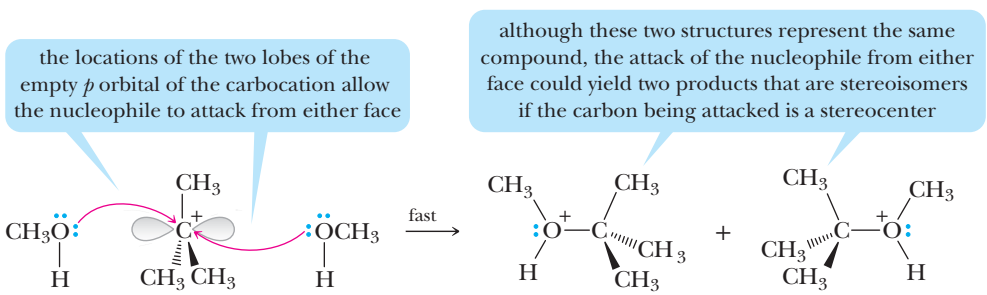
An S_N1 Reaction

STEP 1: *Break a bond to form a more stable ion or molecule.*
The ionization of a C—X bond forms a 3° carbocation intermediate:



A carbocation intermediate; carbon is trigonal planar

STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction of the carbocation intermediate (an electrophile) with methanol (a nucleophile) gives an oxonium ion. Attack by the nucleophile occurs with equal probability from either face of the planar carbocation intermediate.



STEP 3: *Take a proton away.*
Proton transfer from the oxonium ion to methanol (the solvent) completes the reaction and gives *tert*-butyl methyl ether:

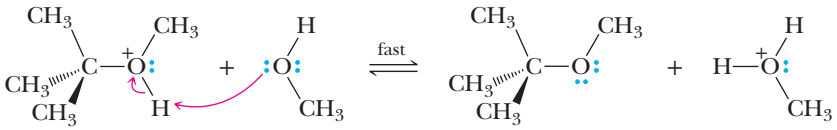


Figure 7.2 shows an energy diagram for the S_N1 reaction of 2-bromo-2-methyl propane and methanol. There is one transition state leading to formation of the carbocation intermediate in Step 1 and a second transition state for reaction of the carbocation intermediate with methanol in Step 2 to give the oxonium ion. The reaction leading to formation of the carbocation intermediate crosses the higher energy barrier and is, therefore, the rate-determining step.

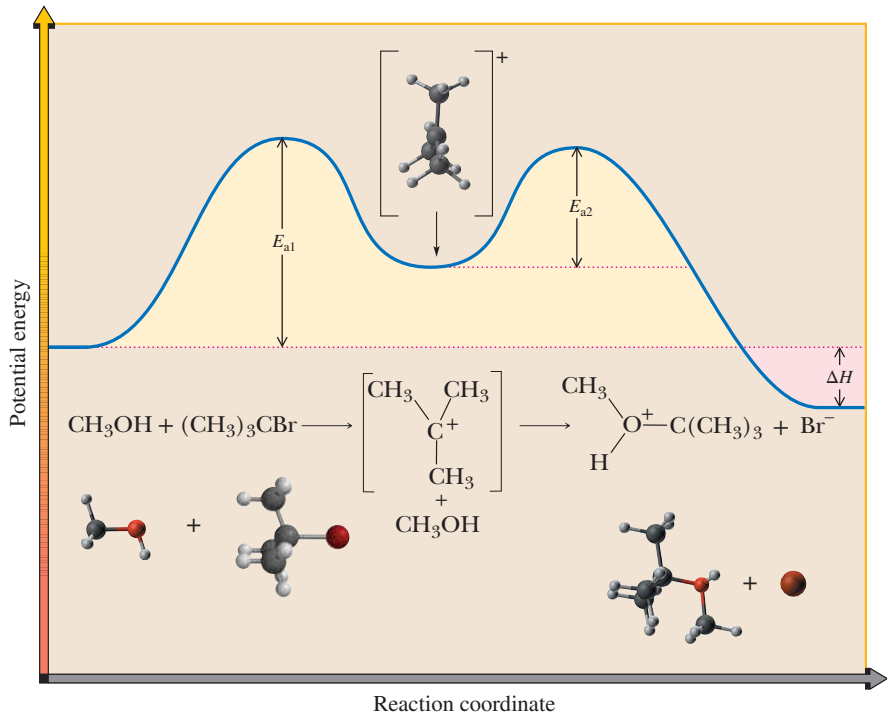
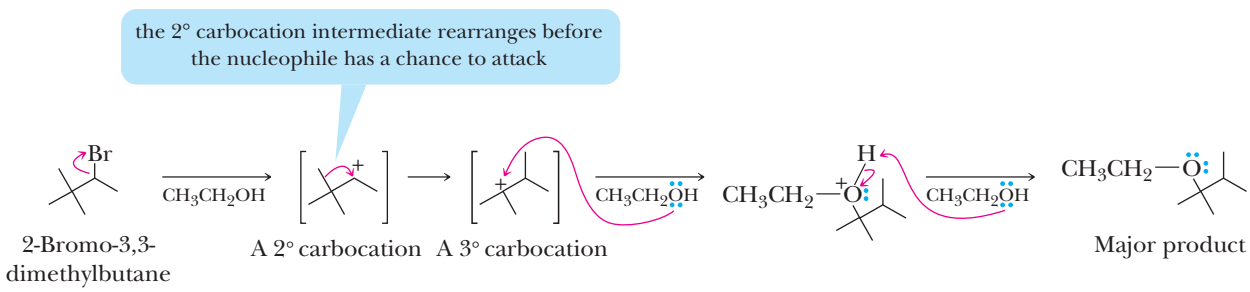
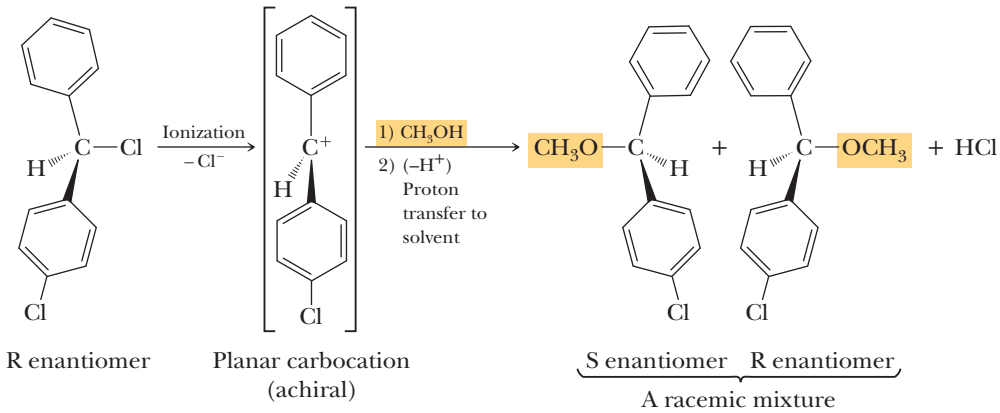


FIGURE 7.2 An energy diagram for the S_N1 reaction of 2-bromo-2-methylpropane and methanol. There is one transition state leading to formation of the carbocation intermediate in Step 1 and a second transition state for the reaction of the carbocation intermediate with methanol in Step 2. Step 1 crosses the higher energy barrier and is, therefore, rate determining.

If an S_N1 reaction is carried out on a 2° haloalkane, a 2° carbocation is formed as an intermediate. Recall from Section 5.4 that a 2° carbocation can undergo a rearrangement to form a more stable 3° carbocation. This is illustrated in the solvolysis reaction of 2-bromo-3,3-dimethylbutane in ethanol.



If an S_N1 reaction is carried out at a tetrahedral stereocenter, the major product is a racemic mixture. We can illustrate this result with the following example: Upon ionization, the R enantiomer forms an achiral carbocation intermediate. Attack by the nucleophile from the left face of the carbocation intermediate gives the S enantiomer; attack from the right face gives the R enantiomer. Because attack by the nucleophile occurs with equal probability from either face of the planar carbocation intermediate, the R and S enantiomers are formed in equal amounts, and the product is a racemic mixture.



7.5 What Determines Whether S_N1 or S_N2 Predominates?

Let us now examine some of the experimental evidence on which these two contrasting mechanisms are based. As we do so, we consider the following questions:

1. What effect does the structure of the nucleophile have on the rate of reaction?
2. What effect does the structure of the haloalkane have on the rate of reaction?
3. What effect does the structure of the leaving group have on the rate of reaction?
4. What is the role of the solvent?

A. Structure of the Nucleophile

Nucleophilicity is a kinetic property, which we measure by relative rates of reaction. We can establish the relative nucleophilicities for a series of nucleophiles by measuring the rate at which each displaces a leaving group from a haloalkane—for example, the rate at which each displaces bromide ion from bromoethane in ethanol at 25°C:

$$CH_3CH_2Br + NH_3 \rightarrow CH_3CH_2NH_3^+ + Br^-$$

From these studies, we can then make correlations between the structure of the nucleophile and its **relative nucleophilicity**. Table 7.2 lists the types of nucleophiles we deal with most commonly in this text.

Relative nucleophilicity The relative rates at which a nucleophile reacts in a reference nucleophilic substitution reaction.

Because the nucleophile participates in the rate-determining step in an S_N2 reaction, the better the nucleophile, the more likely it is that the reaction will occur by that mechanism. The nucleophile does not participate in the rate-determining step for an S_N1 reaction. Thus, an S_N1 reaction can, in principle, occur at approximately the same rate with any of the common nucleophiles, regardless of their relative nucleophilicities.

B. Structure of the Haloalkane

S_N1 reactions are governed mainly by **electronic factors**, namely, the relative stabilities of carbocation intermediates. S_N2 reactions, by contrast, are governed mainly by **steric factors**, and their transition states are particularly sensitive to crowding about the site of reaction. The distinction is as follows:

Steric factors The ability of groups, because of their size, to hinder access to a reaction site within a molecule.

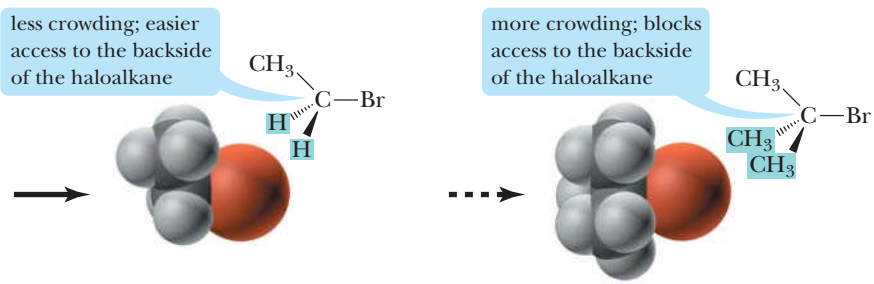
1. *Relative stabilities of carbocations.* As we learned in Section 5.3A, 3° carbocations are the most stable carbocations, requiring the lowest activation energy for their formation, whereas 1° carbocations are the least stable, requiring the highest activation energy for their formation. In fact, 1° carbocations are so unstable that they have never been observed in solution. Therefore, 3° haloalkanes are most likely to react by carbocation formation; 2° haloalkanes are less likely to react in this manner, and methyl and 1° haloalkanes never react in that manner.
2. *Steric hindrance.* To complete a substitution reaction, the nucleophile must approach the substitution center and begin to form a new covalent bond to it. If we compare the ease of approach by the nucleophile to the substitution center of a 1° haloalkane with that of a

TABLE 7.2 Examples of Common Nucleophiles and Their Relative Effectiveness

Effectiveness as a Nucleophile	Nucleophile
Increasing nucleophilicity ↑	
good	Br^-, I^-
good	CH_3S^-, RS^-
good	HO^-, CH_3O^-, RO^-
moderate	Cl^-, F^-
moderate	CH_3CO^-, RCO^-
moderate	CH_3SH, RSH, R_2S
moderate	NH_3, RNH_2, R_2NH, R_3N
poor	H_2O
poor	CH_3OH, ROH
poor	CH_3COH, $RCOH$

the table shows that negatively charged species are better nucleophiles than neutral species

3° haloalkane, we see that the approach is considerably easier in the case of the 1° haloalkane. Two hydrogen atoms and one alkyl group screen the backside of the substitution center of a 1° haloalkane. In contrast, three alkyl groups screen the backside of the substitution center of a 3° haloalkane. This center in bromoethane is easily accessible to a nucleophile, while there is extreme crowding around the substitution center in 2-bromo-2-methylpropane:



Bromoethane (Ethyl bromide) 2-Bromo-2-methylpropane (*tert*-Butyl bromide)

Given the competition between electronic and steric factors, we find that 3° haloalkanes react by an S_N1 mechanism because 3° carbocation intermediates are particularly stable and because the backside approach of a nucleophile to the substitution center in a 3° haloalkane is hindered by the three groups surrounding it; 3° haloalkanes never react by an S_N2 mechanism. Halomethanes and 1° haloalkanes have little crowding around the substitution center and react by an S_N2 mechanism; they never react by an S_N1 mechanism, because methyl and primary carbocations are so unstable. Secondary haloalkanes may react by either an S_N1 or an S_N2 mechanism, depending on the nucleophile and solvent. The competition between electronic and steric factors and their effects on relative rates of nucleophilic substitution reactions of haloalkanes are summarized in Figure 7.3.

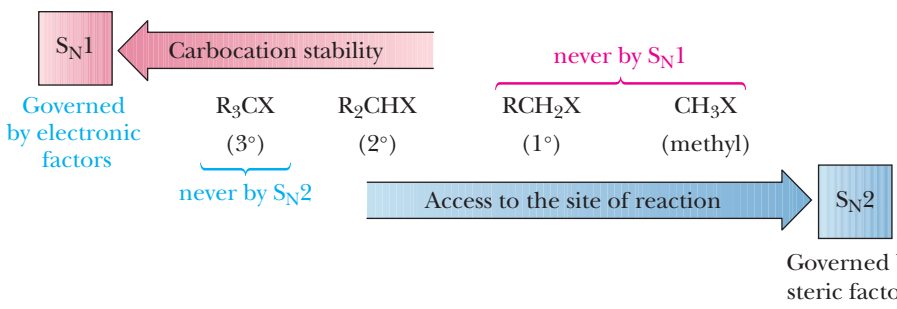
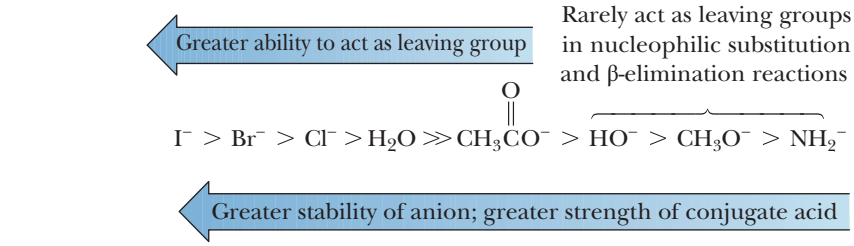


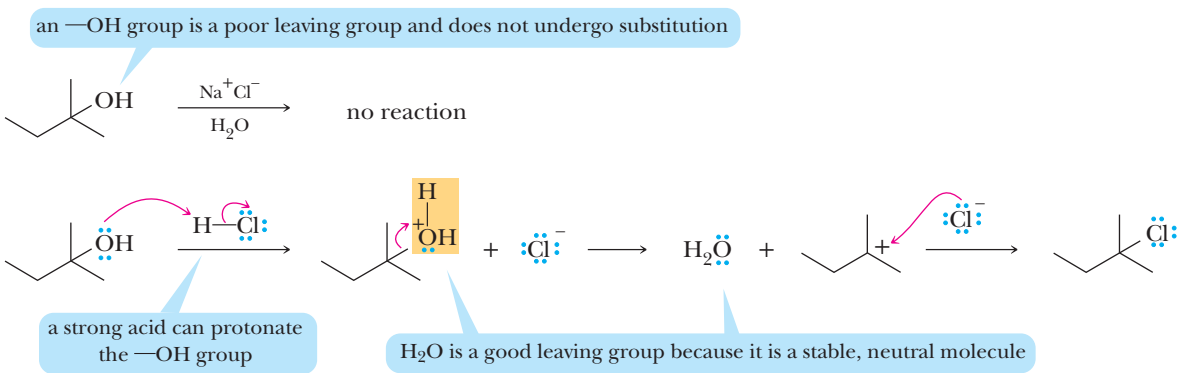
FIGURE 7.3 Effect of electronic and steric factors in competition between S_N1 and S_N2 reactions of haloalkanes.

C. The Leaving Group

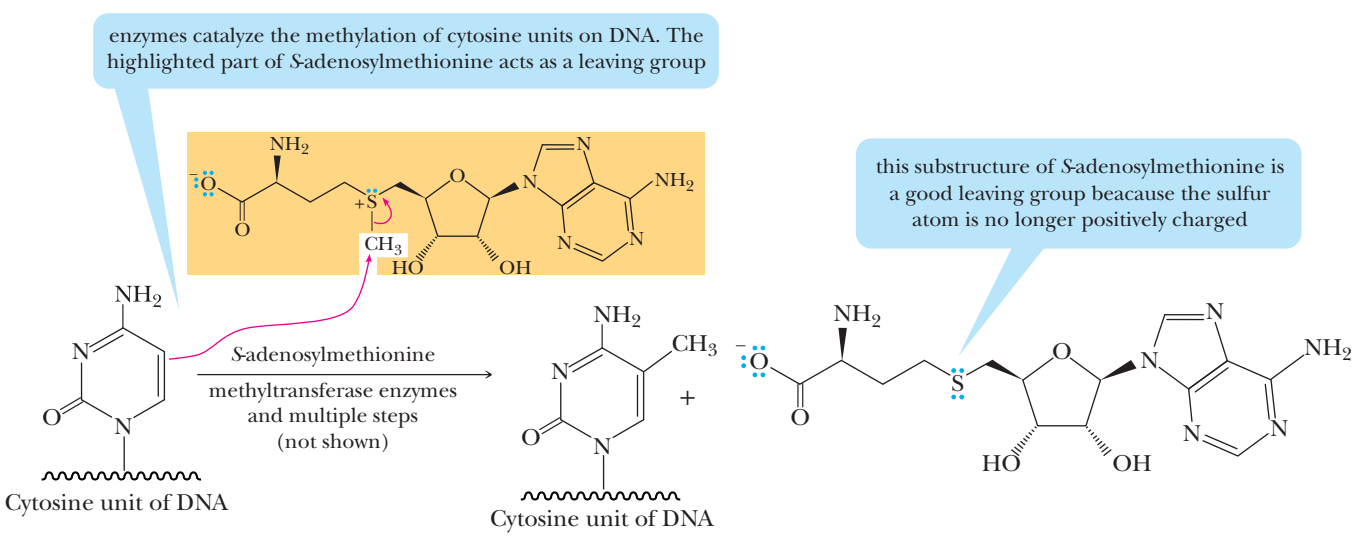
In the transition state for nucleophilic substitution on a haloalkane, the halogen leaving group develops a partial negative charge in both S_N1 and S_N2 reactions. The halogens Cl^-, Br^-, and I^- make good leaving groups because their size and electronegativity help to stabilize the resulting negative charge. Thus, the ability of a group to function as a leaving group is related to how stable it is as an anion. The most stable anions and the best leaving groups are the conjugate bases of strong acids. We can use the information on the relative strengths of organic and inorganic acids in Table 2.1 to determine which anions are the best leaving groups:



The best leaving groups in this series are the halogens I^-, Br^-, and Cl^-. Hydroxide ion (OH^-), methoxide ion (CH_3O^-), and amide ion (NH_2^-) are such poor leaving groups that they rarely, if ever, are displaced in nucleophilic aliphatic substitution reactions. H_2O can act as a leaving group if an —OH group of an alcohol is first protonated by an acid.



One important example of leaving group stability is found in the methylation of DNA, a process common in all mammals and involved in a variety of biological processes including X-chromosome inactivation in females, inheritance, and carcinogenesis. In DNA methylation, enzymes catalyze the attack of a cytosine unit of DNA on the methyl group of *S*-adenosylmethionine (SAM). All but the methyl group of SAM acts as a leaving group and is able to do so because the positive sulfur atom initially bonded to the methyl group becomes uncharged, making the sulfur atom more stable than before.



We will have more to say about leaving groups other than the halides in subsequent chapters.

D. The Solvent

Solvents provide the medium in which reactants are dissolved and in which nucleophilic substitution reactions take place. Common solvents for these reactions are divided into two groups: **protic** and **aprotic.**

Protic solvent A hydrogen bond donor solvent as, for example, water, ethanol, and acetic acid. We define hydrogen bond donors as compounds containing hydrogens that can participate in H-bonding.

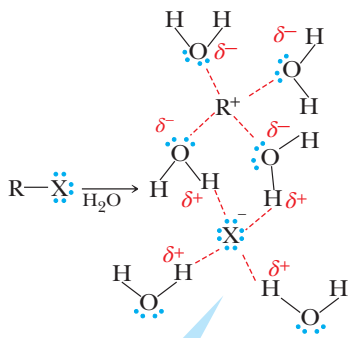
Protic solvents contain —OH groups and are hydrogen-bond donors. Common protic solvents for nucleophilic substitution reactions are water, low-molecular-weight alcohols, and low-molecular-weight carboxylic acids (Table 7.3). Each is able to solvate both the anionic and cationic components of ionic compounds by electrostatic interaction between its partially negatively charged oxygen(s) and the cation and between its partially positively charged hydrogen(s) and the anion. These same properties aid in the ionization of C—X bonds to give an X^- anion and a carbocation; thus, protic solvents are good solvents in which to carry out S_N1 reactions.

Aprotic solvents A solvent that cannot serve as a hydrogen bond donor as, for example, acetone, diethyl ether, and dichloromethane.

Aprotic solvents do not contain —OH groups and cannot function as hydrogen-bond donors. They are unable to promote the formation of a carbocation because the leaving group would be unsolvated. Therefore aprotic solvents cannot be used in S_N1 reactions. Table 7.4 lists the aprotic solvents most commonly used for nucleophilic substitution reactions. Dimethyl sulfoxide and acetone are polar aprotic solvents; dichloromethane and diethyl ether are less polar aprotic solvents. The aprotic solvents listed in the table are particularly good ones in which to carry out S_N2 reactions. Because polar aprotic solvents are able to solvate only cations and not anions, they allow for "naked" and highly reactive anions as nucleophiles when used with ionic nucleophiles such as Na^+CN^-, Na^+OH^-, and so on.

TABLE 7.3 Common Protic Solvents

Protic Solvent	Structure	Polarity of Solvent	Notes
Water	H_2O	Increasing	These solvents favor S_N1 reactions. The greater the polarity of the solvent, the easier it is to form carbocations in it because both the carbocation and the negatively charged leaving group can be solvated.
Formic acid	HCOOH		
Methanol	CH_3OH		
Ethanol	CH_3CH_2OH		
Acetic acid	CH_3COOH		

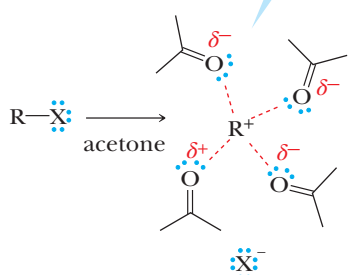


polar protic solvents can solvate both the anion and the cation components of the S_N1 reaction

TABLE 7.4 Common Aprotic Solvents

Aprotic Solvent	Structure	Polarity of Solvent	Notes
Dimethyl sulfoxide (DMSO)	$CH_3\overset{\overset{O}{\|}}{S}CH_3$	Increasing	These solvents favor S_N2 reactions. Although solvents at the top of this list are polar, the formation of carbocations in them is far more difficult than in protic solvents because the anionic leaving group cannot be solvated by these solvents.
Acetone	$CH_3\overset{\overset{O}{\|}}{C}CH_3$		
Dichloromethane	CH_2Cl_2		
Diethyl ether	$(CH_3CH_2)_2O$		

polar aprotic solvents, like acetone, can only solvate cations effectively, making it *unlikely* for a leaving group to break its bond to carbon and undergo an S_N1 reaction



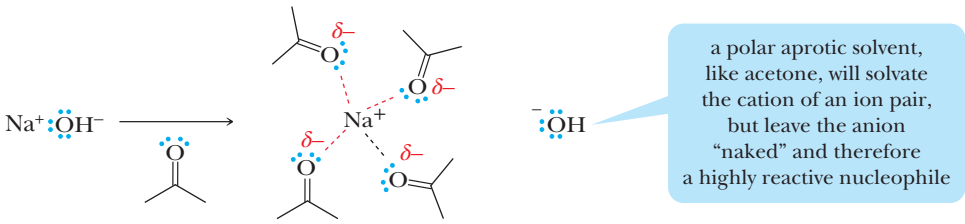


Table 7.5 summarizes the factors favoring S_N1 or S_N2 reactions; it also shows the change in configuration when nucleophilic substitution takes place at a stereocenter.

TABLE 7.5 Summary of S_N1 versus S_N2 Reactions of Haloalkanes

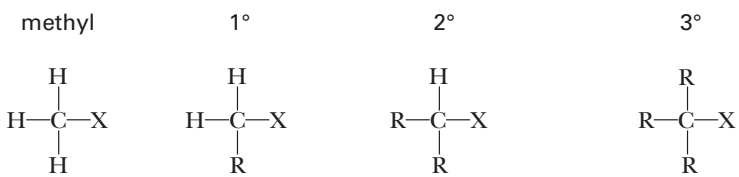
Type of Haloalkane	S_N2	S_N1
Methyl CH_3X	**S_N2 is favored.**	**S_N1 does not occur.** The methyl cation is so unstable that it is never observed in solution.
Primary RCH_2X	**S_N2 is favored.**	**S_N1 does not occur.** Primary carbocations are so unstable that they are not observed in solution.
Secondary R_2CHX	**S_N2 is favored** in aprotic solvents with good nucleophiles.	**S_N1 is favored** in protic solvents with poor nucleophiles.
Tertiary R_3CX	**S_N2 does not occur,** because of steric hindrance around the substitution center.	**S_N1 is favored** because of the ease of formation of tertiary carbocations.
Substitution at a stereocenter	**Inversion of configuration.** The nucleophile attacks the stereocenter from the side opposite the leaving group.	**Racemization.** The carbocation intermediate is planar, and attack by the nucleophile occurs with equal probability from either side.

HOW TO 7.4

Predict the Type of Substitution Reaction a Haloalkane Will Undergo

(a) Identify and assess the stability of the potential leaving group. A substitution reaction will not occur unless there is a good leaving group.

(b) Classify the structure of the haloalkane. Methyl and primary haloalkanes do not undergo S_N1 reactions, while tertiary haloalkanes do not undergo S_N2 reactions.



(c) Identify the nucleophile and assess its relative nucleophilicity. S_N2 reactions are favored with good nucleophiles and rarely occur with poor nucleophiles. S_N1 reactions can occur with both poor and moderate nucleophiles, but receive competition from the S_N2 mechanism in the presence of good nucleophiles.

(d) Identify and classify the solvent. A polar protic solvent is required for an S_N1 reaction. Polar aprotic solvents favor S_N2 reactions, although S_N2 reactions can also occur in protic solvents.

(e) If no single factor eliminates or mandates either substitution mechanism, try to determine whether these factors collectively favor the predominance of one mechanism over the other.

EXAMPLE 7.4

Answer the following questions:

(a) The rate of a substitution reaction of a haloalkane is unchanged when the nucleophile is switched from hydroxide to ammonia. What type of substitution reaction does this haloalkane likely undergo?

(b) When (*R*)-2-bromobutane is reacted with diethylamine, $(CH_3CH_2)_2NH$, the reaction solution gradually loses optical activity. What type of substitution mechanism is in operation in this reaction?

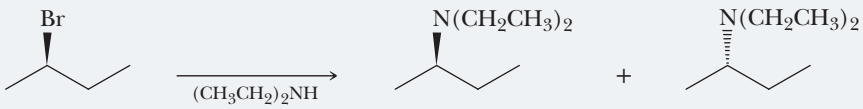
STRATEGY

It is important to remember the details that go along with each of the two substitution mechanisms. In an S_N1 reaction, look for (1) the rate of the reaction to be unaffected by the type or the concentration of the nucleophile or (2) the formation of two products (often enantiomers if stereochemistry exists at the reacting carbon). In an S_N2 reaction, look for (1) the rate of the reaction to be dependent on the type or the concentration of the nucleophile or (2) the formation of only one product.

SOLUTION

(a) S_N1. Hydroxide ion is a better nucleophile than ammonia. S_N1 reactions are unaffected by the effectiveness of the nucleophile. If the reaction were to occur by an S_N2 mechanism, we would expect reaction with the better nucleophile to result in a faster reaction.

(b) S_N1. Diethylamine is a moderate nucleophile and likely favors the S_N1 mechanism. This is confirmed by the stereochemical data, because an S_N2 reaction would yield only the S enantiomer because of the required backside attack. The loss of optical activity most likely indicates that a carbocation intermediate is formed, followed by the attack of the nucleophile to form equal amounts of the enantiomers shown.



(*R*)-2-bromobutane (*R*) (*S*)

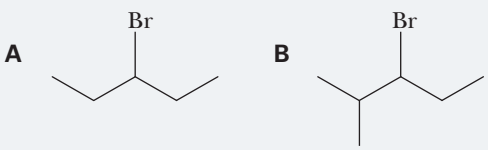
See problems 7.20, 7.23, 7.27

PROBLEM 7.4

Answer the following questions:

(a) Potassium cyanide, KCN, reacts faster than trimethylamine, $(CH_3)_3N$, with 1-chloropentane. What type of substitution mechanism does this haloalkane likely undergo?

(b) Compound A reacts faster with dimethylamine, $(CH_3)_2NH$, than compound B. What does this reveal about the relative ability of each haloalkane to undergo S_N2? S_N1?

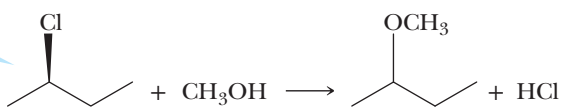


7.6 How Can S_N1 and S_N2 Be Predicted Based on Experimental Conditions?

Predictions about the mechanism for a particular nucleophilic substitution reaction must be based on considerations of the structure of the haloalkane, the nucleophile, and the solvent. Following are analyses of three such reactions:

Nucleophilic Substitution Example 1

before continuing, try to predict whether these reactions proceed by an S_N1 or S_N2 mechanism



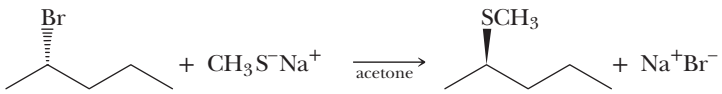
R enantiomer

Methanol is a polar protic solvent and a good one in which to form carbocations. 2-Chlorobutane ionizes in methanol to form a 2° carbocation intermediate. Methanol is a weak nucleophile. From this analysis, we predict that reaction is by an S_N1 mechanism. The 2° carbocation intermediate (an electrophile) then reacts with methanol (a nucleophile) followed by proton transfer to give the observed product. The product is formed as a 50:50 mixture of R and S configurations; that is, it is formed as a racemic mixture.

Nucleophilic Substitution Example 2

This is a 1° bromoalkane in the presence of iodide ion, a good nucleophile. Because 1° carbocations are so unstable, they never form in solution, and an S_N1 reaction is not possible. Dimethyl sulfoxide (DMSO), a polar aprotic solvent, is a good solvent in which to carry out S_N2 reactions. From this analysis, we predict that reaction is by an S_N2 mechanism.

Nucleophilic Substitution Example 3

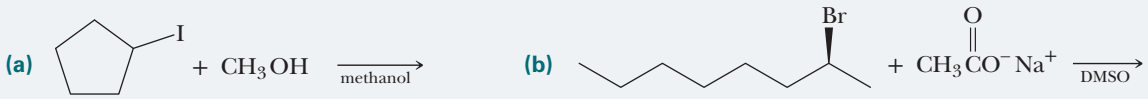


S enantiomer

Bromine ion is a good leaving group on a 2° carbon. The methylsulfide ion is a good nucleophile. Acetone, a polar aprotic solvent, is a good medium in which to carry out S_N2 reactions, but a poor medium in which to carry out S_N1 reactions. We predict that reaction is by an S_N2 mechanism and that the product formed has the R configuration.

EXAMPLE 7.5

Write the expected product for each nucleophilic substitution reaction, and predict the mechanism by which the product is formed:

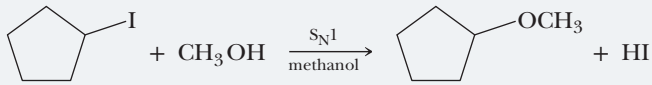


STRATEGY

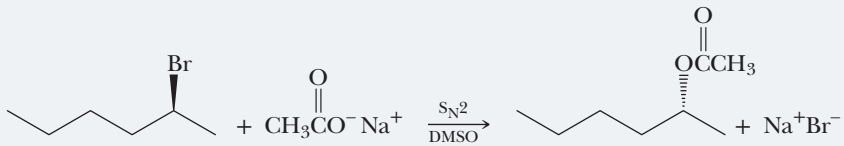
Determine whether the electrophile's reaction center is 1°, 2°, or 3°. Then assess the nucleophilicity of the nucleophile. If it is poor, then the reaction will most likely proceed by an S_N1 mechanism, provided that there exists a polar protic solvent and the reaction center is 2° or 3°. If there is a good nucleophile, then the reaction will most likely proceed by an S_N2 mechanism, provided that the reaction center is 1° or 2°. If the nucleophile is moderate, focus on the solvent polarity and reaction center of the electrophile. Remember that S_N1 mechanisms only occur in polar protic solvents.

SOLUTION

(a) Methanol is a poor nucleophile. It is also a polar protic solvent that is able to solvate carbocations. Ionization of the carbon–iodine bond forms a 2° carbocation intermediate. We predict an S_N1 mechanism:



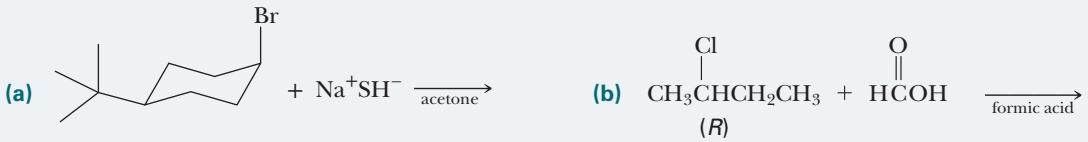
(b) Bromide is a good leaving group on a 2° carbon. Acetate ion is a moderate nucleophile. DMSO is a particularly good solvent for S_N2 reactions. We predict substitution by an S_N2 mechanism with inversion of configuration at the stereocenter:



See problems 7.23, 7.25–7.28, 7.34, 7.35

PROBLEM 7.5

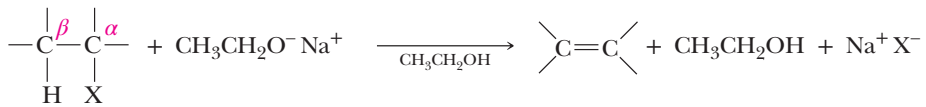
Write the expected product for each nucleophilic substitution reaction, and predict the mechanism by which the product is formed:



7.7 What Are the Products of β-Elimination?

Dehydrohalogenation Removal of —H and —X from adjacent carbons; a type of β-elimination.

In this section, we study a type of β-elimination called **dehydrohalogenation**. In the presence of a strong base, such as hydroxide ion or ethoxide ion, halogen can be removed from one carbon of a haloalkane and hydrogen from an adjacent carbon to form a C—C double bond:



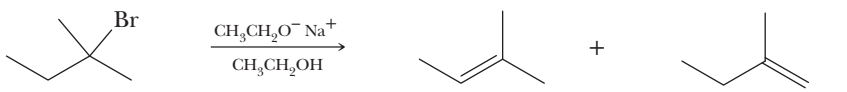
A haloalkane Base An alkene

As the equation shows, we call the carbon bearing the halogen the *α-carbon* and the adjacent carbon the *β-carbon*.

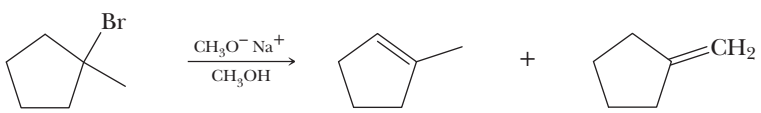
Because most nucleophiles can also act as bases and vice versa, it is important to keep in mind that β-elimination and nucleophilic substitution are competing reactions. In this section, we concentrate on β-elimination. In Section 7.9, we examine the results of competition between the two.

Common strong bases used for β-elimination are OH^-, OR^-, and NH_2^-. Following are three examples of base-promoted β-elimination reactions:

1- Bromooctane Potassium *tert*-butoxide 1- Octene



2-Bromo-2-methylbutane 2-Methyl-2-butene (major product) 2-Methyl-1-butene



1-Bromo-1-methylcyclopentane 1-Methylcyclopentene (major product) Methylenecyclopentane

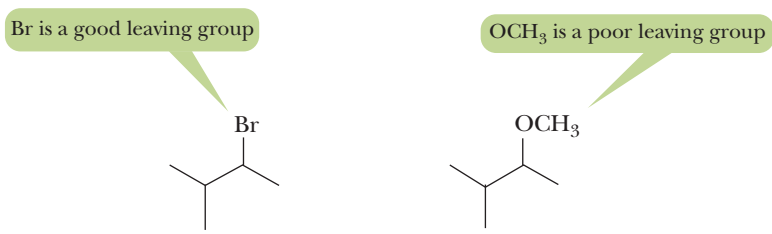
In the first example, the base is shown as a reactant. In the second and third examples, the base is a reactant, but is shown over the reaction arrow. Also in the second and third examples, there are nonequivalent β-carbons, each bearing a hydrogen; therefore, two alkenes are possible from each β-elimination reaction. In each case, the major product of these and most other β-elimination reactions is the more substituted (and therefore the more stable—see Section 5.6) alkene. We say that each reaction follows **Zaitsev's rule** or, alternatively, that each undergoes Zaitsev elimination, to honor the chemist who first made this generalization.

Zaitsev's rule A rule stating that the major product from a β-elimination reaction is the most stable alkene; that is, the major product is the alkene with the greatest number of substituents on the carbon–carbon double bond.

Complete an Elimination Reaction

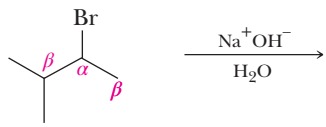
HOW TO 7.5

(a) Identify and assess the leaving group. An elimination reaction will not occur unless there is a good leaving group.

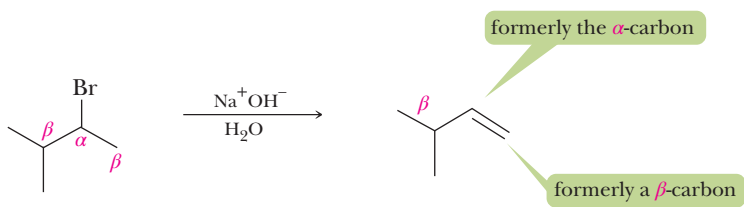


(b) Label the carbon bonded to the leaving group as "α" (alpha).

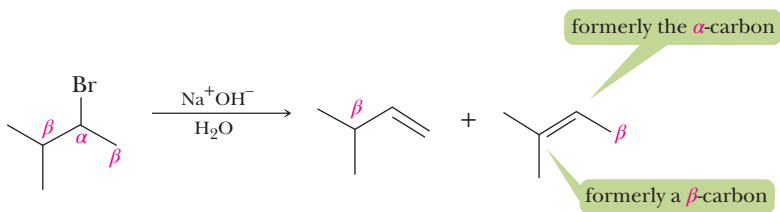
(c) Label any carbon bonded to the α-carbon as "β" (beta). *Note*: Only do so if the β-carbon is bonded to a hydrogen atom.



(d) Remove the leaving group and a β-hydrogen from the molecule and place a new double bond between the α and β-carbons. This forms a β-elimination product.

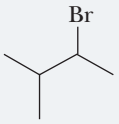


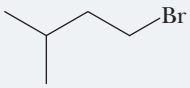
(e) Repeat Step (d) above for any other β-carbons to form a different β-elimination product.

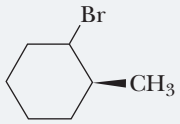


EXAMPLE 7.6

Predict the β-elimination product(s) formed when each bromoalkane is treated with sodium ethoxide in ethanol (if two might be formed, predict which is the major product):

(a) 

(b) 

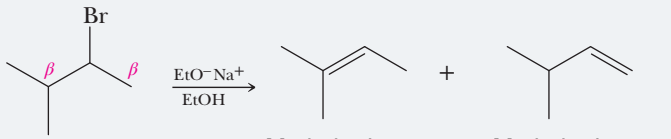
(c) 

STRATEGY

Label the carbon bonded to the halogen as α. Then label any carbons next to the α-carbon as β. If the β-carbon is bonded to at least one hydrogen, remove that hydrogen and the halogen and draw a C—C double bond between the α- and β-carbons. Start over and repeat this process for any other β-carbons that meet this criteria. Each time you are able to do this will result in an elimination product.

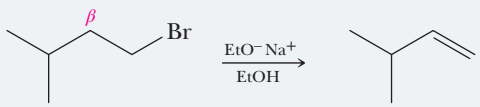
SOLUTION

(a) There are two nonequivalent β-carbons in this bromoalkane, and two alkenes are possible. 2-Methyl-2-butene, the more substituted alkene, is the major product:



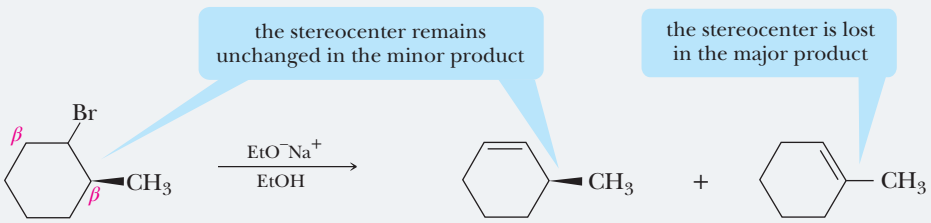
2-Methyl-2-butene (major product) 3-Methyl-1-butene

(b) There is only one β-carbon in this bromoalkane, and only one alkene is possible.



3-Methyl-1-butene

(c) There are two nonequivalent β-carbons in this cyclic bromoalkane, and two alkenes are possible. 1-Methylcyclohexene, the more substituted alkene, is the major product:

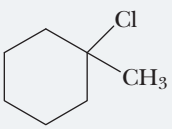


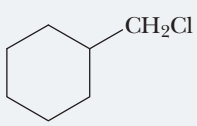
(*S*)-3-Methylcyclohexene 1-Methylcyclohexene (major product)

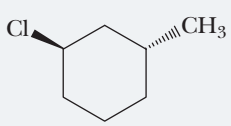
See problems 7.36–7.38

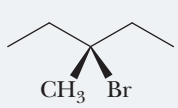
PROBLEM 7.6

Predict the β-elimination products formed when each chloroalkane is treated with sodium ethoxide in ethanol (if two products might be formed, predict which is the major product):

(a) 

(b) 

(c) 

(d) 

7.8 What Are the E1 and E2 Mechanisms for β-Elimination?

There are two limiting mechanisms of β-elimination reactions. A fundamental difference between them is the timing of the bond-breaking and bond-forming steps. Recall that we made this same statement about the two limiting mechanisms for nucleophilic substitution reactions in Section 7.4.

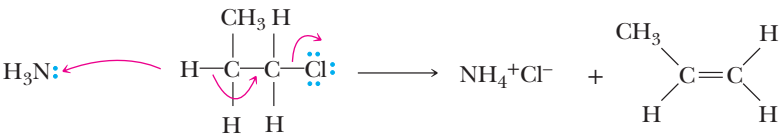
Draw Mechanisms

HOW TO 7.6

Remember that curved arrow notation always shows the arrow originating from a bond or from a lone pair of electrons.

Correct use of curved arrows...

Incorrect use of curved arrows...



A. E1 Mechanism

At one extreme, breaking of the C—X bond is complete before any reaction occurs with base to lose a hydrogen and before the carbon–carbon double bond is formed. This mechanism is designated **E1**, where *E* stands for *e*limination and *1* stands for a *uni*molecular reaction; only *one* species, in this case the haloalkane, is involved in the rate-determining step. The rate law for an E1 reaction has the same form as that for an S_N1 reaction:

$$\text{Rate} = k[\text{haloalkane}]$$

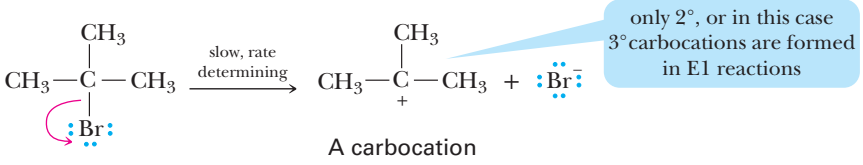
The mechanism for an E1 reaction is illustrated by the reaction of 2-bromo-2-methylpropane to form 2-methylpropene. In this two-step mechanism, the rate-determining step is the ionization of the carbon–halogen bond to form a carbocation intermediate (just as it is in an S_N1 mechanism).

Mechanism

E1 Reaction of 2-Bromo-2-methylpropane

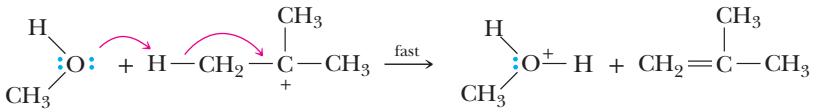
STEP 1: *Break a bond.*

Rate-determining ionization of the C—Br bond gives a carbocation intermediate:



STEP 2: *Take away a proton.*

Proton transfer from the carbocation intermediate to methanol (which in this instance is both the solvent and a reactant) gives the alkene:



B. E2 Mechanism

At the other extreme is a concerted process. In an **E2** reaction, *E* stands for *e*limination, and *2* stands for *bi*molecular. Because the base removes a β-hydrogen at the same time the C—X bond is broken to form a halide ion, the rate law for the rate-determining step is dependent on both the haloalkane and the base:

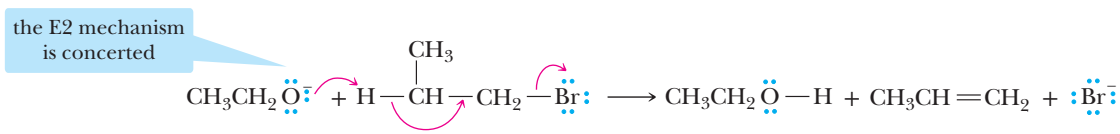
$$\text{Rate} = k[\text{haloalkane}][\text{base}]$$

The stronger the base, the more likely it is that the E2 mechanism will be in operation. We illustrate an E2 mechanism by the reaction of 1-bromopropane with sodium ethoxide.

Mechanism

E2 Reaction of 1-Bromopropane

In the E2 mechanism we (1) take away a proton and (2) break a bond to form a stable ion or molecule. Proton transfer to the base, formation of the carbon–carbon double bond, and the ejection of bromide ion occur simultaneously; that is, all bond-forming and bond-breaking steps occur at the same time.



For both E1 and E2 reactions, the major product is that formed in accordance with Zaitsev's rule (Section 7.7) as illustrated by this E2 reaction:

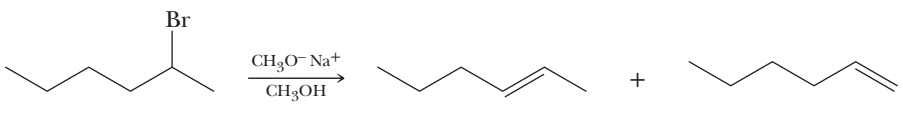


Table 7.6 summarizes these generalizations about β-elimination reactions of haloalkanes.

TABLE 7.6 Summary of E1 versus E2 Reactions of Haloalkanes

Haloalkane	E1	E2
Primary RCH_2X	E1 does not occur. Primary carbocations are so unstable that they are never observed in solution.	E2 is favored.
Secondary R_2CHX	Main reaction with weak bases such as H_2O and ROH.	Main reaction with strong bases such as OH^- and OR^-.
Tertiary R_3CX	Main reaction with weak bases such as H_2O and ROH.	Main reaction with strong bases such as OH^- and OR^-.

HOW TO 7.7

Predict the Type of β-Elimination Reaction a Haloalkane Will Undergo

(a) Classify the structure of the haloalkane. Primary haloalkanes will not undergo E1 reactions. Secondary and tertiary haloalkanes will undergo both E1 and E2 reactions.

(b) Identify and assess the base. E2 reactions are favored with strong bases and rarely occur with weak bases. E2 reactions can occur in any solvent. E1 reactions can occur with both weak and strong bases, but require polar protic solvents to stabilize the carbocation formed in the first step of the reaction.

EXAMPLE 7.7

Predict whether each β-elimination reaction proceeds predominantly by an E1 or E2 mechanism, and write a structural formula for the major organic product:

(a) $CH_3CCH_2CH_3$ (Cl) + Na^+OH^- $\xrightarrow[H_2O]{80\ ^\circ C}$

(b) $CH_3CCH_2CH_3$ (Cl) $\xrightarrow{CH_3COOH}$

STRATEGY

Identify the solvent and the base. If the base is strong, an E2 mechanism is favored to occur. If the base is weak and the solvent is polar protic, then an E1 mechanism is favored to occur.

SOLUTION

(a) A 3° chloroalkane is heated with NaOH, a strong base. Elimination by an E2 reaction predominates, giving 2-methyl-2-butene as the major product:

$$CH_3CCH_2CH_3\ (Cl) + Na^+OH^- \xrightarrow[H_2O]{80\ ^\circ C} CH_3C{=}CHCH_3 + Na^+Br^- + H_2O$$

(b) A 3° chloroalkane dissolved in acetic acid, a solvent that promotes the formation of carbocations, forms a 3° carbocation that then loses a proton to give 2-methyl-2-butene as the major product. The reaction is by an E1 mechanism:

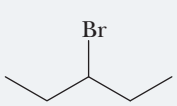
acetic acid acts as the solvent and as a weak base

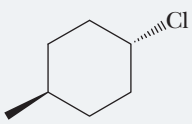
$$CH_3CCH_2CH_3\ (Cl) \xrightarrow{CH_3COOH} CH_3C{=}CHCH_3 + CH_3COOH_2^+Cl^-$$

See problems 7.36–7.38

PROBLEM 7.7

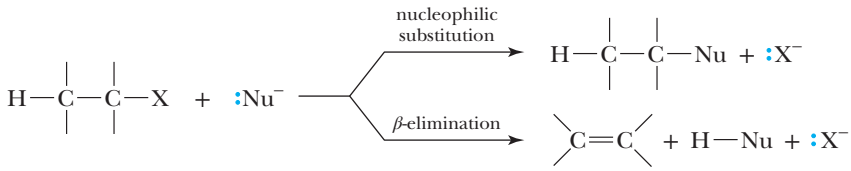
Predict whether each elimination reaction proceeds predominantly by an E1 or E2 mechanism, and write a structural formula for the major organic product:

(a)  + $CH_3O^-\ Na^+$ $\xrightarrow{\text{methanol}}$

(b)  + Na^+OH^- $\xrightarrow{\text{acetone}}$

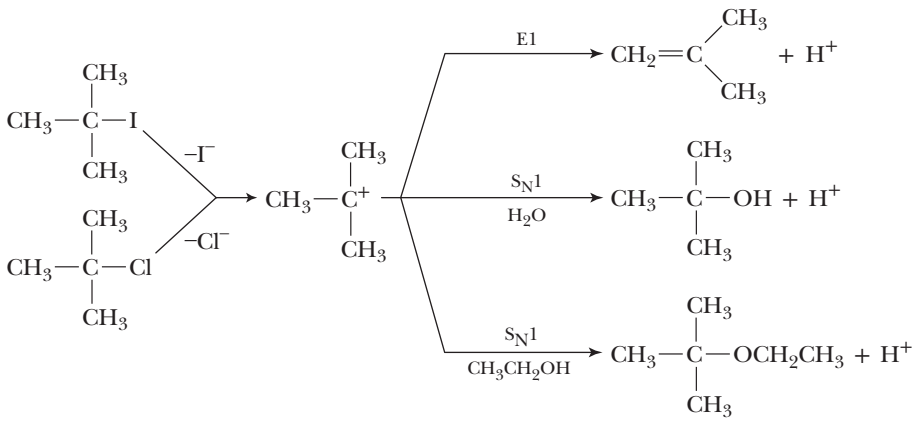
7.9 When Do Nucleophilic Substitution and β-Elimination Compete?

Thus far, we have considered two types of reactions of haloalkanes: nucleophilic substitution and β-elimination. Many of the nucleophiles we have examined—for example, hydroxide ion and alkoxide ions—are also strong bases. Accordingly, nucleophilic substitution and β-elimination often compete with each other, and the ratio of products formed by these reactions depends on the relative rates of the two reactions:



A. S_N1-versus-E1 Reactions

Reactions of secondary and tertiary haloalkanes in polar protic solvents give mixtures of substitution and elimination products. In both reactions, Step 1 is the formation of a carbocation intermediate. This step is then followed by either (1) the loss of a hydrogen to give an alkene (E1) or (2) reaction with solvent to give a substitution product (S_N1). In polar protic solvents, the products formed depend only on the structure of the particular carbocation. For example, *tert*-butyl chloride and *tert*-butyl iodide in 80% aqueous ethanol both react with solvent, giving the same mixture of substitution and elimination products:



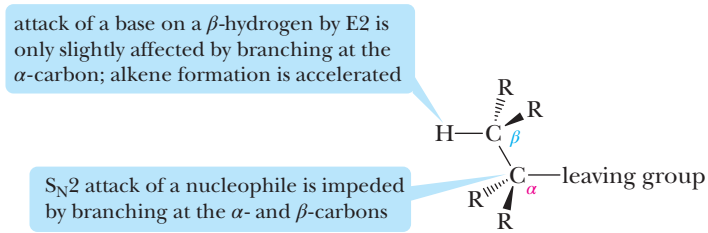
Because iodide ion is a better leaving group than chloride ion, *tert*-butyl iodide reacts over 100 times faster than *tert*-butyl chloride. Yet the ratio of products is the same.

B. S_N2-versus-E2 Reactions

It is considerably easier to predict the ratio of substitution to elimination products for reactions of haloalkanes with reagents that act as both nucleophiles and bases. The guiding principles are as follows:

1. Branching at the α-carbon or β-carbon(s) increases steric hindrance about the α-carbon and significantly retards S_N2 reactions. By contrast, branching at the α-carbon or β-carbon(s) increases the rate of E2 reactions because of the increased stability of the alkene product.

2. The greater the nucleophilicity of the attacking reagent, the greater is the S_N2-to-E2 ratio. Conversely, the greater the basicity of the attacking reagent, the greater is the E2-to-S_N2 ratio.



Primary halides react with bases/nucleophiles to give predominantly substitution products. With strong bases, such as hydroxide ion and ethoxide ion, a percentage of the product is formed by an E2 reaction, but it is generally small compared with that formed by an S_N2 reaction. With strong, bulky bases, such as *tert*-butoxide ion, the E2 product becomes the major product. Tertiary halides react with all strong bases/good nucleophiles to give only elimination products.

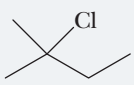
Secondary halides are borderline, and substitution or elimination may be favored, depending on the particular base/nucleophile, solvent, and temperature at which the reaction is carried out. Elimination is favored with strong bases/good nucleophiles—for example, hydroxide ion and ethoxide ion. Substitution is favored with weak bases/poor nucleophiles—for example, acetate ion. Table 7.7 summarizes these generalizations about substitution versus elimination reactions of haloalkanes.

TABLE 7.7 Summary of Substitution versus Elimination Reactions of Haloalkanes

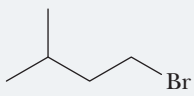
Halide	Reaction	Comments
Methyl	S_N2	The only substitution reactions observed.
CH_3X	~~S_N1~~	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
Primary RCH_2X	S_N2	The main reaction with strong bases such as OH^- and EtO^-. Also, the main reaction with good nucleophiles/weak bases, such as I^- and CH_3COO^-.
	E2	The main reaction with strong, bulky bases, such as potassium *tert*-butoxide.
	~~S_N1/E1~~	Primary cations are never formed in solution; therefore, S_N1 and E1 reactions of primary halides are never observed.
Secondary R_2CHX	S_N2	The main reaction with weak bases/good nucleophiles, such as I^- and CH_3COO^-.
	E2	The main reaction with strong bases/good nucleophiles, such as OH^- and $CH_3CH_2O^-$.
	S_N1/E1	Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.
Tertiary R_3CX	~~S_N2~~	S_N2 reactions of tertiary halides are never observed because of the extreme crowding around the 3° carbon.
	E2	Main reaction with strong bases, such as HO^- and RO^-.
	S_N1/E1	Main reactions with poor nucleophiles/weak bases.

EXAMPLE 7.8

Predict whether each reaction proceeds predominantly by substitution (S_N1 or S_N2) or elimination (E1 or E2) or whether the two compete, and write structural formulas for the major organic product(s):

(a) 

$+ \ Na^+OH^- \xrightarrow[H_2O]{80\ ^\circ C}$

(b) 

$+ \ (C_2H_5)_3N \xrightarrow[CH_2Cl_2]{30\ ^\circ C}$

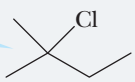
STRATEGY

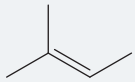
First, determine whether the reagent acts predominantly as a base or a nucleophile. If it is a weak base but a good nucleophile, substitution is more likely to occur. If the reagent is a strong base but a poor nucleophile, elimination is more likely to occur. When the reagent can act equally as both a base and a nucleophile, use other factors to decide whether substitution or elimination predominates. These include the degree of substitution about the reacting center (1° haloalkanes will not undergo E1 or S_N1 reactions, 3° haloalkanes will not undergo S_N2 reactions) or type of solvent (E1 and S_N1 reactions require polar protic solvents).

SOLUTION

(a) A 3° halide is heated with a strong base/good nucleophile. Elimination by an E2 reaction predominates to give 2-methyl-2-butene as the major product:

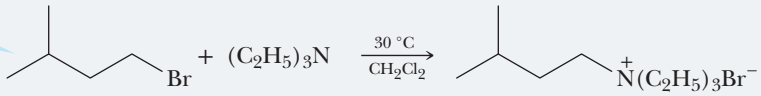
a strong base/good nucleophile favors E2/S_N2. However, 3° halides cannot undergo S_N2 reactions



$+ \ Na^+OH^- \xrightarrow[H_2O]{80\ ^\circ C}$

$+ \ Na^+Cl^- + H_2O$

(b) Reaction of a 1° halide with triethylamine, a moderate nucleophile/weak base, gives substitution by an S_N2 reaction:

1° halides cannot undergo E1/S_N1 reactions. The base is not strong enough to undergo an E2 reaction

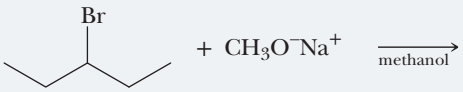


See problem 7.43

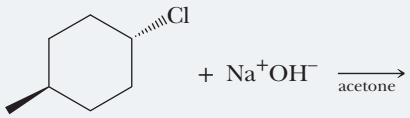
PROBLEM 7.8

Predict whether each reaction proceeds predominantly by substitution (S_N1 or S_N2) or elimination (E1 or E2) or whether the two compete, and write structural formulas for the major organic product(s):

(a)



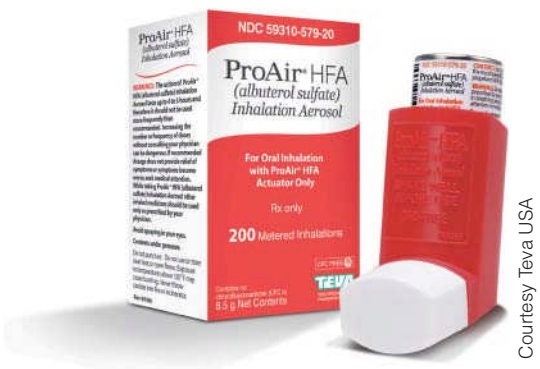
(b)



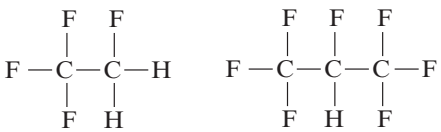
Chemical Connections 7B

THE EFFECT OF CHLOROFLUOROCARBON LEGISLATION ON ASTHMA SUFFERERS

The Montreal Protocol on Substances That Deplete the Ozone Layer was proposed in 1987 and enacted in 1989. As a result of this treaty, and its many revisions, the phaseout of CFCs and many other substances harmful to the ozone layer has been achieved in many industrialized nations. However, the Montreal Protocol provided exceptions for products in which the use of CFCs was essential because no viable alternatives existed. One such product was albuterol metered-dose inhalers, which use CFCs as propellants to deliver the drug and are used by asthma patients worldwide. In the United States, this exemption from the Montreal Protocol expired in December 2008, thanks to the Clean Air Act and the availability of another type of propellant known as hydrofluoroalkanes (HFAs). One drawback of HFA-equipped inhalers is that of cost; HFA inhalers cost three to six times as much as CFC-enabled inhalers because generic versions do not yet exist. This has sparked concerns from patients, physicians, and patients' rights groups over the ability of the nearly 23 million people in the United States who suffer from asthma to obtain treatment. Other differences include taste, smell, temperature of inhalant upon ejection, and effectiveness in colder climates and higher altitudes (HFAs are more effective under these conditions than CFCs). These practical differences are a result of the absence of chlorine in HFAs versus in CFCs, and are an excellent example of how changes in chemical structure can affect the properties of molecules and their ultimate applications in society.



Courtesy Teva USA



HFA-134a HFA-227

Hydrofluoroalkanes used in CFC-free medical inhalers

Question

Would you expect HFA-134a or HFA-227 to undergo an S_N1 reaction? An S_N2 reaction? Why or why not?

SUMMARY OF KEY QUESTIONS

7.1 How Are Haloalkanes Named?

- In the IUPAC system, halogen atoms are named as fluoro-, chloro-, bromo-, or iodo-substituents and are listed in alphabetical order with other substituents.
- In the common system, **haloalkanes** are named **alkyl halides**, where the name is derived by naming the alkyl group followed by the name of the halide as a separate word (e.g., methyl chloride).
- Compounds of the type CHX_3 are called **haloforms**.

7.2 What Are the Characteristic Reactions of Haloalkanes?

- Haloalkanes undergo **nucleophilic substitution** reactions and **β-elimination** reactions.
- In substitution reactions, the halogen is replaced by a reagent known as a **nucleophile**. A nucleophile is any molecule or ion with an unshared pair of electrons that can be donated to another atom or ion to form a new covalent bond; alternatively, a nucleophile is a Lewis base.
- In elimination reactions, the halogen and an adjacent hydrogen are removed to form an alkene.

7.3 What Are the Products of Nucleophilic Aliphatic Substitution Reactions?

- The product of a nucleophilic substitution reaction varies depending on the nucleophile used in the reaction. For example, when the nucleophile is hydroxide (HO^-), the product will be an alcohol (ROH).
- Nucleophilic substitution reactions can be used to transform haloalkanes into alcohols, ethers, thiols, sulfides, alkyl iodides, and alkyl ammonium ions, to name a few.

7.4 What Are the S_N2 and S_N1 Mechanisms for Nucleophilic Substitution?

- An **S_N2** reaction occurs in one step. The departure of the **leaving group** is assisted by the incoming nucleophile, and both nucleophile and leaving group are involved in the transition state. S_N2 reactions are stereoselective; reaction at a stereocenter proceeds with **inversion of configuration**.
- An **S_N1** reaction occurs in two steps. Step 1 is a slow, rate-determining ionization of the C—X bond to form a carbocation intermediate, followed in Step 2 by its rapid reaction with a nucleophile to complete the substitution. For S_N1 reactions taking place at a stereocenter, the major reaction occurs with **racemization**.

7.5 What Determines Whether S_N1 or S_N2 Predominates?

- The stability of the leaving group. The ability of a group to function as a leaving group is related to its stability as an anion. The most stable anions and the best leaving groups are the conjugate bases of strong acids.
- The **nucleophilicity** of a reagent. Nucleophilicity is measured by the rate of its reaction in a reference nucleophilic substitution.
- The structure of the haloalkane. S_N1 reactions are governed by **electronic factors**, namely, the relative stabilities of carbocation intermediates. S_N2 reactions are governed by **steric factors**, namely, the degree of crowding around the site of substitution.
- The nature of the solvent. **Protic solvents** contain —OH groups, interact strongly with polar molecules and ions, and are good solvents in which to form carbocations. Protic solvents favor S_N1 reactions. **Aprotic solvents** do not contain —OH groups. Common aprotic solvents are **dimethyl sulfoxide**, acetone, diethyl ether, and dichloromethane. Aprotic solvents do not interact as strongly with polar molecules and ions, and carbocations are less likely to form in them. Aprotic solvents favor S_N2 reactions.
- A nonhalogenated compound with a good leaving group can, like haloalkanes, undergo substitution reactions.
- Halogens make good leaving groups because either their size (as in I^- or Br^-) or electronegativity (Cl^-) helps to stabilize the resulting negative charge. F^- is not a good leaving group because HF is a weak acid. HCl, HBr, and HI are strong acids, making their halide anions weak bases.
- The ability of a group to function as a leaving group is related to how stable it is as an anion.
- The most stable anions and the best leaving groups are the conjugate bases of strong acids.

7.6 How Can S_N1 and S_N2 Be Predicted Based on Experimental Conditions?

- Predictions about the mechanism for a particular nucleophilic substitution reaction must be based on considerations of the structure of the haloalkane, the nucleophile, the leaving group, and the solvent.

7.7 What Are the Products of β-Elimination?

- **Dehydrohalogenation**, a type of β-elimination reaction, is the removal of H and X from adjacent carbon atoms, resulting in the formation of a carbon–carbon double bond.

- A β-elimination that gives the most highly substituted alkene is called **Zaitsev elimination**.

7.8 What Are the E1 and E2 Mechanisms for β-Elimination?

- An **E1** reaction occurs in two steps: breaking the C—X bond to form a carbocation intermediate, followed by the loss of an H^+ to form the alkene.
- An **E2** reaction occurs in one step: reaction with the base to remove an H^+, formation of the alkene, and departure of the leaving group, all occurring simultaneously.

7.9 When Do Nucleophilic Substitution and β-Elimination Compete?

- Many of the nucleophiles we have examined—for example, hydroxide ion and alkoxide ions—are also strong bases. As a result, nucleophilic substitution and β-elimination often compete with each other, and the ratio of products formed by these reactions depends on the relative rates of the two reactions.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. An S_N1 reaction can result in two products that are stereoisomers. (7.4)
2. In naming halogenated compounds, "haloalkane" is the IUPAC form of the name while "alkyl halide" is the common form of the name. (7.1)
3. A substitution reaction results in the formation of an alkene. (7.3)
4. Ethoxide ion ($CH_3CH_2O^-$) can act as a base and as a nucleophile in its reaction with bromocyclohexane. (7.2)
5. The rate law of the E2 reaction is dependent on just the haloalkane concentration. (7.8)
6. The mechanism of the S_N1 reaction involves the formation of a carbocation intermediate. (7.4)
7. Polar protic solvents are required for E1 or S_N1 reactions to occur. (7.9)
8. OH^- is a better leaving group than Cl^-. (7.5)
9. When naming haloalkanes with more than one type of halogen, numbering priority is given to the halogen with the higher mass. (7.1)
10. S_N2 reactions prefer good nucleophiles, while S_N1 reactions proceed with most any nucleophile. (7.5)
11. The stronger the base, the better is the leaving group. (7.5)
12. S_N2 reactions are more likely to occur with 2° haloalkanes than with 1° haloalkanes. (7.9)
13. A solvolysis reaction is a reaction performed without solvent. (7.4)
14. The degree of substitution at the reaction center affects the rate of an S_N1 reaction but not an S_N2 reaction. (7.5)
15. A reagent must possess a negative charge to react as a nucleophile. (7.3)
16. Elimination reactions favor the formation of the more substituted alkene. (7.7)
17. The best leaving group is one that is unstable as an anion. (7.5)
18. In the S_N2 reaction, the nucleophile attacks the carbon from the side opposite that of the leaving group. (7.4)
19. Only haloalkanes can undergo substitution reactions. (7.5)
20. All of the following are polar aprotic solvents: acetone, DMSO, ethanol. (7.5)

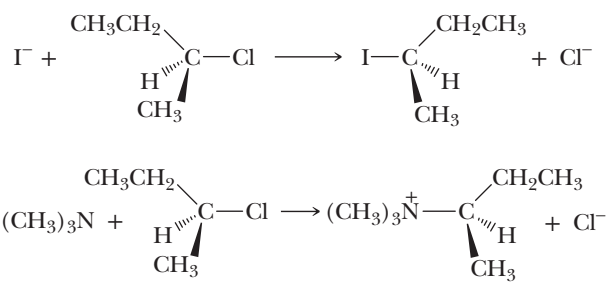
Answers: (1) T (2) T (3) F (4) T (5) F (6) T (7) T (8) F (9) F (10) T
(11) F (12) F (13) F (14) F (15) F (16) T (17) F (18) T (19) F (20) F

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

KEY REACTIONS

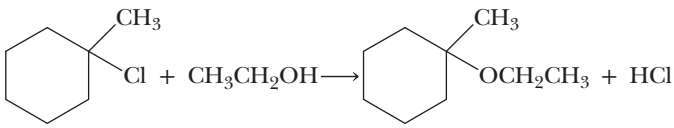
1. Nucleophilic Aliphatic Substitution: S_N2 (Section 7.4A)

S_N2 reactions occur in one step, and both the nucleophile and the leaving group are involved in the transition state of the rate-determining step. The nucleophile may be negatively charged or neutral. S_N2 reactions result in an inversion of configuration at the reaction center. They are accelerated in polar aprotic solvents, compared with polar protic solvents. S_N2 reactions are governed by steric factors, namely, the degree of crowding around the site of reaction.



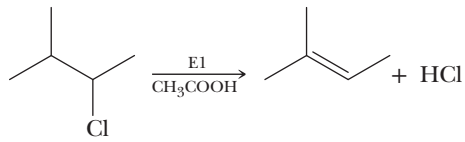
2. Nucleophilic Aliphatic Substitution: S_N1 (Section 7.4B)

An S_N1 reaction occurs in two steps. Step 1 is a slow, rate-determining ionization of the C—X bond to form a carbocation intermediate, followed in Step 2 by its rapid reaction with a nucleophile to complete the substitution. Reaction at a stereocenter gives a racemic product. S_N1 reactions are governed by electronic factors, namely, the relative stabilities of carbocation intermediates:



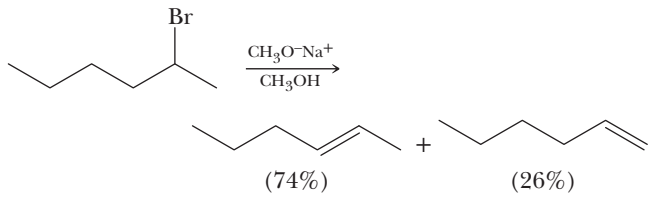
3. β-Elimination: E1 (Section 7.8A)

E1 reactions involve the elimination of atoms or groups of atoms from adjacent carbons. Reaction occurs in two steps and involves the formation of a carbocation intermediate:



4. β-Elimination: E2 (Section 7.8B)

An E2 reaction occurs in one step: reaction with base to remove a hydrogen, formation of the alkene, and departure of the leaving group, all occurring simultaneously:



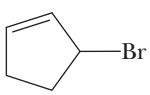
PROBLEMS

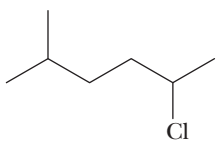
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 7.1 Nomenclature

7.9 Write the IUPAC name for each compound: **(See Example 7.1)**

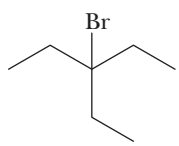
(a) $CH_2{=}CF_2$

(b) 

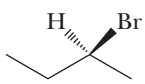
(c) 

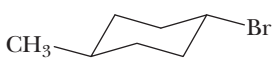
(d) $Cl(CH_2)_6Cl$

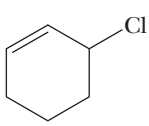
(e) CF_2Cl_2

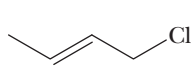
(f) 

7.10 Write the IUPAC name for each compound (be certain to include a designation of configuration, where appropriate, in your answer): **(See Example 7.1)**

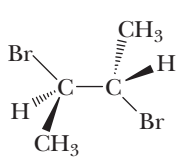
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

7.11 Draw a structural formula for each compound (given are IUPAC names): **(See Example 7.1)**

(a) 3-Bromopropene

(b) (*R*)-2-Chloropentane

(c) meso-3,4-Dibromohexane

(d) *trans*-1-Bromo-3-isopropylcyclohexane

(e) 1,2-Dichloroethane

(f) Bromocyclobutane

7.12 Draw a structural formula for each compound (given are common names): **(See Example 7.1)**

(a) Isopropyl chloride

(b) *sec*-Butyl bromide

(c) Allyl iodide

(d) Methylene chloride

(e) Chloroform

(f) *tert*-Butyl chloride

(g) Isobutyl chloride

7.13 Which compounds are 2° alkyl halides?

(a) Isobutyl chloride

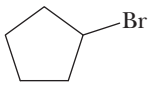
(b) 2-Iodooctane

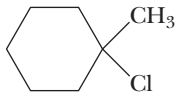
(c) *trans*-1-Chloro-4-methylcyclohexane

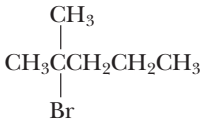
(d) 3-bromo-3-methylpentane

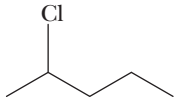
Synthesis of Alkyl Halides

7.14 What alkene or alkenes and reaction conditions give each alkyl halide in good yield? (*Hint*: Review Chapter 5.) **(See Example 5.2)**

(a) 

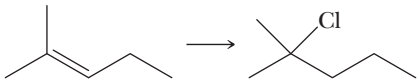
(c) 

(b) 

(d) 

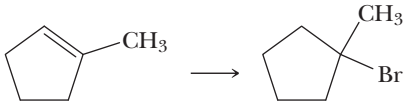
racemic

7.15 Show reagents and conditions that bring about these conversions: **(See Example 5.2)**

(a) 

(b) $CH_3CH_2CH{=}CH_2 \longrightarrow CH_3CH_2\underset{\displaystyle I}{\underset{|}{C}}HCH_3$

(c) $CH_3CH{=}CHCH_3 \rightarrow CH_3\underset{\displaystyle CL}{\underset{|}{C}}HCH_2CH_3$

(d) 

SECTIONS 7.2–7.6 Nucleophilic Aliphatic Substitution

7.16 Write structural formulas for these common organic solvents:

(a) Dichloromethane
(b) Acetone
(c) Ethanol
(d) Diethyl ether
(e) Dimethyl sulfoxide
(f) *tert*-Butyl alcohol

7.17 Arrange these protic solvents in order of increasing polarity:

(a) H_2O
(b) CH_3CH_2OH
(c) CH_3OH
(d) CH_3NH_2

7.18 Arrange these aprotic solvents in order of increasing polarity:

(a) Acetone
(b) Pentane
(c) Diethyl ether

7.19 From each pair, select the better nucleophile:

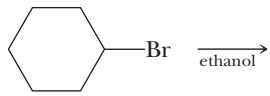
(a) H_2O or OH^-
(b) CH_3COO^- or OH^-
(c) CH_3SH or CH_3S^-

7.20 Which statements are true for S_N2 reactions of haloalkanes? **(See Example 7.4)**

(a) Both the haloalkane and the nucleophile are involved in the transition state.
(b) The reaction proceeds with inversion of configuration at the substitution center.
(c) The reaction proceeds with retention of optical activity.
(d) The order of reactivity is 3° > 2° > 1° > methyl.
(e) The nucleophile must have an unshared pair of electrons and bear a negative charge.
(f) The greater the nucleophilicity of the nucleophile, the greater is the rate of reaction.

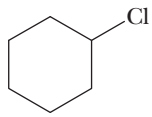
7.21 Complete these S_N2 reactions: **(See Examples 7.3, 7.5)**

(a) $Na^+I^- + CH_3CH_2CH_2Cl \xrightarrow[\text{acetone}]{}$

(b) $NH_3 +$  $\xrightarrow[\text{ethanol}]{}$

(c) $CH_3CH_2O^-Na^+ + CH_2{=}CHCH_2Cl \xrightarrow[\text{ethanol}]{}$

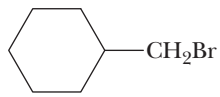
7.22 Complete these S_N2 reactions: **(See Examples 7.3, 7.5)**

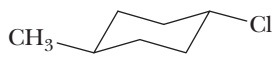
(a)  $+ CH_3\overset{\displaystyle O}{\overset{\|}{C}}O^- Na^+ \xrightarrow[\text{ethanol}]{}$

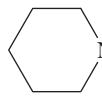
(b) $CH_3\underset{\displaystyle I}{\underset{|}{C}}HCH_2CH_3 + CH_3CH_2S^-Na^+ \xrightarrow[\text{acetone}]{}$

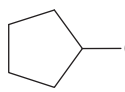
(c) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2Br + Na^+I^- \xrightarrow[\text{acetone}]{}$

(d) $(CH_3)_3N + CH_3I \xrightarrow[\text{acetone}]{}$

(e)  $+ CH_3O^-Na^+ \xrightarrow[\text{methanol}]{}$

(f)  $+ CH_3S^-Na^+ \xrightarrow[\text{ethanol}]{}$

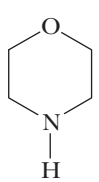
(g)  $+ CH_3(CH_2)_6CH_2Cl \xrightarrow[\text{ethanol}]{}$

(h)  $+ NH_3 \xrightarrow[\text{ethanol}]{}$

7.23 You were told that each reaction in Problem 7.22 proceeds by an S_N2 mechanism. Suppose you were not told the mechanism. Describe how you could conclude, from the structure of the haloalkane, the nucleophile, and the solvent, that each reaction is in fact an S_N2 reaction. **(See Examples 7.4, 7.5)**

7.24 In the following reactions, a haloalkane is treated with a compound that has two nucleophilic sites. Select the more nucleophilic site in each part, and show the product of each S_N2 reaction:

(a) $HOCH_2CH_2NH_2 + CH_3I \xrightarrow[\text{ethanol}]{}$

(b)  $+ CH_3I \xrightarrow[\text{ethanol}]{}$

(c) $HOCH_2CH_2SH + CH_3I \xrightarrow[\text{ethanol}]{}$

7.25 Which statements are true for S_N1 reactions of haloalkanes? **(See Example 7.5)**

(a) Both the haloalkane and the nucleophile are involved in the transition state of the rate-determining step.

(b) The reaction at a stereocenter proceeds with retention of configuration.

(c) The reaction at a stereocenter proceeds with loss of optical activity.

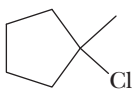
(d) The order of reactivity is 3° > 2° > 1° > methyl.

(e) The greater the steric crowding around the reactive center, the lower is the rate of reaction.

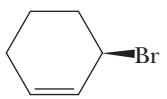
(f) The rate of reaction is greater with good nucleophiles compared with poor nucleophiles.

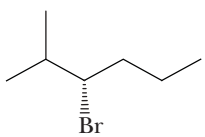
7.26 Draw a structural formula for the product of each S_N1 reaction: **(See Examples 7.3, 7.5)**

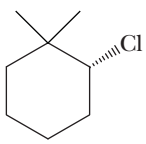
(a) $CH_3\underset{\text{S enantiomer}}{\underset{|}{\overset{Cl}{C}}}HCH_2CH_3 + CH_3CH_2OH \xrightarrow{\text{ethanol}}$

(b)  $+ CH_3OH \xrightarrow{\text{methanol}}$

(c) $CH_3\underset{|}{\overset{CH_3}{C}}Cl + CH_3\overset{O}{\overset{\|}{C}}OH \xrightarrow{\text{acetic acid}}$

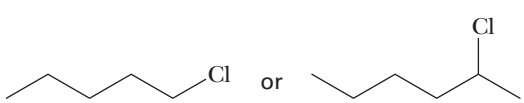
(d)  $+ CH_3OH \xrightarrow{\text{methanol}}$

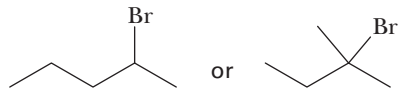
(e)  $+ CH_3CH_2OH \xrightarrow{\text{ethanol}}$

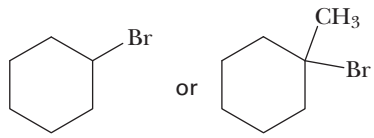
(f)  $+ CH_3\overset{O}{\overset{\|}{C}}OH \xrightarrow{\text{acetic acid}}$

7.27 You were told that each substitution reaction in Problem 7.26 proceeds by an S_N1 mechanism. Suppose that you were not told the mechanism. Describe how you could conclude, from the structure of the haloalkane, the nucleophile, and the solvent, that each reaction is in fact an S_N1 reaction. **(See Examples 7.4, 7.5)**

7.28 Select the member of each pair that undergoes nucleophilic substitution in aqueous ethanol more rapidly: **(See Example 7.5)**

(a) 

(b) 

(c) 

7.29 Propose a mechanism for the formation of the products (but not their relative percentages) in this reaction:

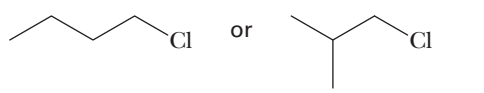
$$CH_3\underset{|}{\overset{CH_3}{C}}Cl \xrightarrow[25\ ^\circ C]{20\%\ H_2O,\ 80\%\ CH_3CH_2OH}$$

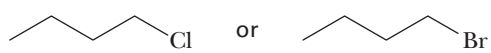
(a)

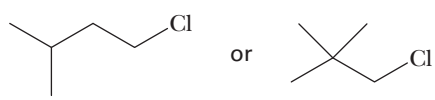
$$\underbrace{CH_3\underset{|}{\overset{CH_3}{C}}OCH_2CH_3}_{85\%} + CH_3\underset{|}{\overset{CH_3}{C}}OH + \underset{15\%}{CH_3\underset{|}{\overset{CH_3}{C}}=CH_2} + HCl$$

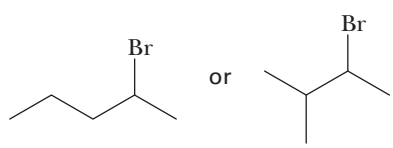
7.30 The rate of reaction in Problem 7.29 increases by 140 times when carried out in 80% water to 20% ethanol, compared with 40% water to 60% ethanol. Account for this difference.

7.31 Select the member of each pair that shows the greater rate of S_N2 reaction with KI in acetone:

(a) 

(b) 

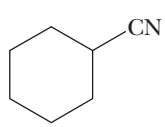
(c) 

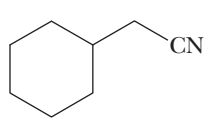
(d) 

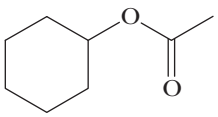
7.32 What hybridization best describes the reacting carbon in the S_N2 transition state?

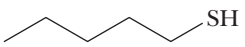
7.33 Haloalkenes such as vinyl bromide, $CH_2{=}CHBr$, undergo neither S_N1 nor S_N2 reactions. What factors account for this lack of reactivity?

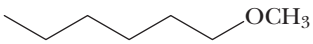
7.34 Show how you might synthesize the following compounds from a haloalkane and a nucleophile: **(See Example 7.5)**

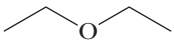
(a) 

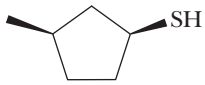
(b) 

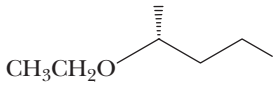
(c) 

(d) 

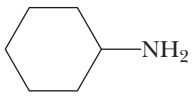
(e) 

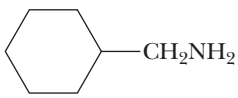
(f) 

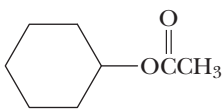
(g) 

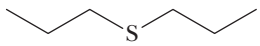
(h) 

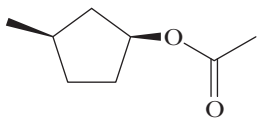
7.35 Show how you might synthesize each compound from a haloalkane and a nucleophile: **(See Example 7.5)**

(a) 

(b) 

(c) 

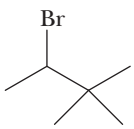
(d) 

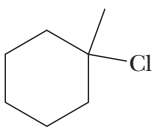
(e) 

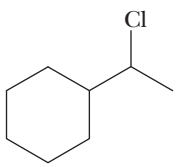
(f) $(CH_3CH_2CH_2CH_2)_2O$

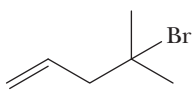
SECTIONS 7.7–7.8 *β*-Eliminations

7.36 Draw structural formulas for the alkene(s) formed by treating each of the following haloalkanes with sodium ethoxide in ethanol. Assume that elimination is by an E2 mechanism. Where two alkenes are possible, use Zaitsev's rule to predict which alkene is the major product: **(See Examples 7.6, 7.7)**

(a) 

(b) 

(c) 

(d) 

7.37 Which of the following haloalkanes undergo dehydrohalogenation to give alkenes that do not show *cis–trans* isomerism? **(See Examples 7.6, 7.7)**

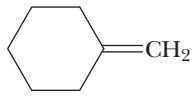
(a) 2-Chloropentane
(b) 2-Chlorobutane
(c) Chlorocyclohexane
(d) Isobutyl chloride

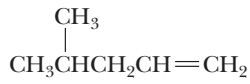
7.38 How many isomers, including *cis–trans* isomers, are possible for the major product of dehydrohalogenation of each of the following haloalkanes? **(See Examples 7.6, 7.7)**

(a) 3-Chloro-3-methylhexane

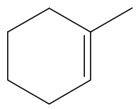
(b) 3-Bromohexane

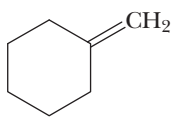
7.39 What haloalkane might you use as a starting material to produce each of the following alkenes in high yield and uncontaminated by isomeric alkenes?

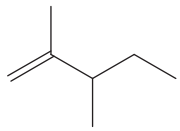
(a) 

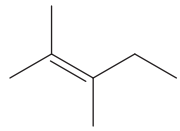
(b) 

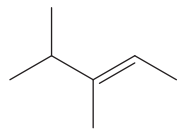
7.40 For each of the following alkenes, draw structural formulas of all chloroalkanes that undergo dehydrohalogenation when treated with KOH to give that alkene as the major product (for some parts, only one chloroalkane gives the desired alkene as the major product; for other parts, two chloroalkanes may work):

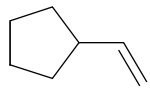
(a) 

(b) 

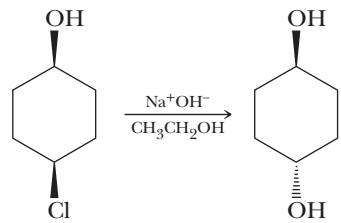
(c) 

(d) 

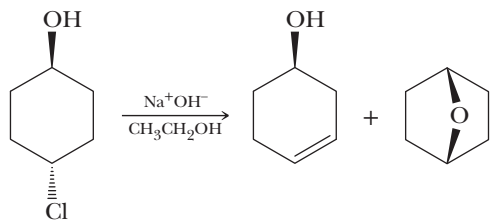
(e) 

(f) 

7.41 When *cis*-4-chlorocyclohexanol is treated with sodium hydroxide in ethanol, it gives only the substitution product *trans*-1,4-cyclohexanediol (1). Under the same experimental conditions, *trans*-4-chlorocyclohexanol gives 3-cyclohexenol (2) and product (3):



cis-4-Chlorocyclohexanol (1)



trans-4-Chlorocyclohexanol (2) (3)

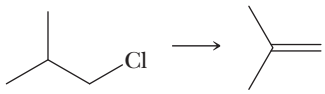
(a) Propose a mechanism for the formation of product (1), and account for its configuration.

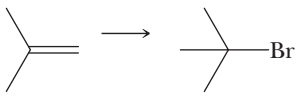
(b) Propose a mechanism for the formation of product (2).

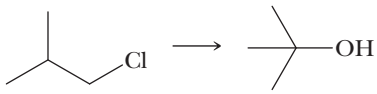
(c) Account for the fact that the product (3) is formed from the *trans* isomer, but not from the *cis* isomer.

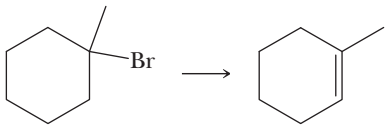
SECTION 7.9 Synthesis and Predict the Product

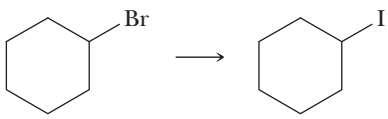
7.42 Show how to convert the given starting material into the desired product (note that some syntheses require only one step, whereas others require two or more steps):

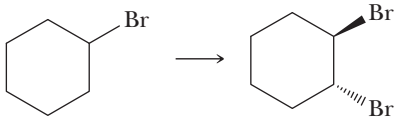
(a) 

(b) 

(c) 

(d) 

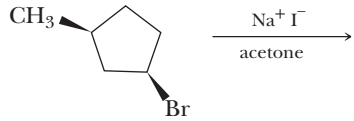
(e) 

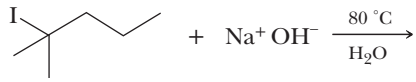
(f) 

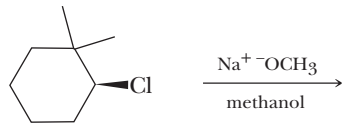
racemic

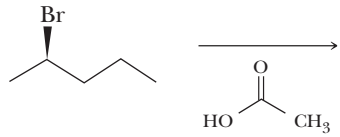
7.43 Complete these reactions by determining the type of reaction and mechanism (S_N1, S_N2, E1, or E2) that they undergo. **(See Example 7.8)**

(a) 

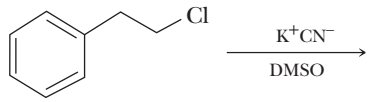
(b) 

(c) 

(d) 

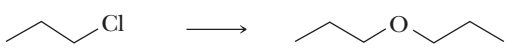
(e) 

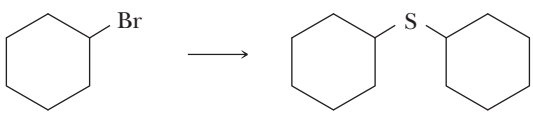
(acetic acid)

(f) 

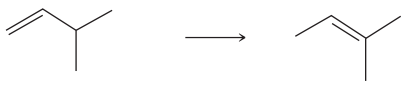
CHEMICAL TRANSFORMATIONS

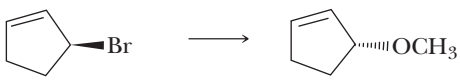
7.44 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.*

(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

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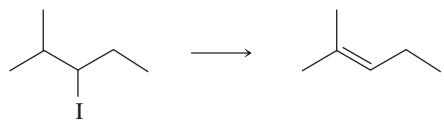
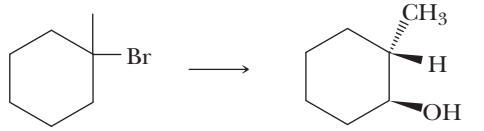
(g) 

(h) 

(i) 

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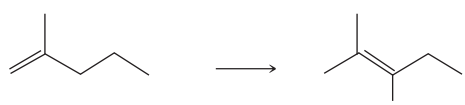
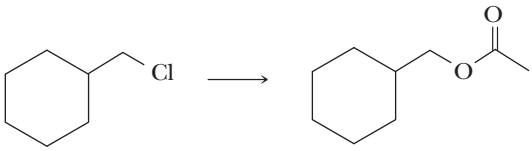
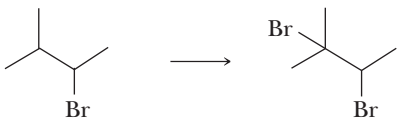
(j) 

(k) 

(l) 

(m) 

(n) 
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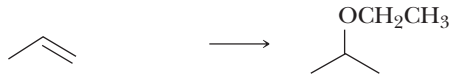
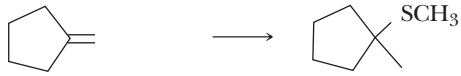
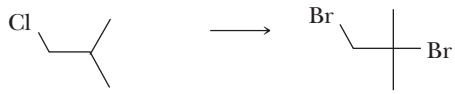
(o) 

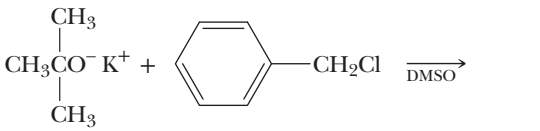
(p) 

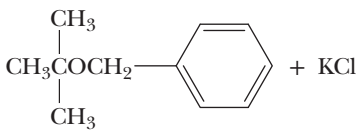
(q) 

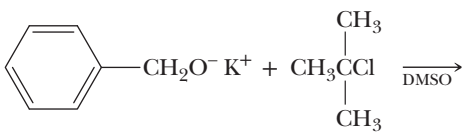
(r) 

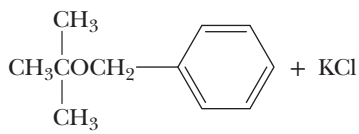
LOOKING AHEAD

7.45 The Williamson ether synthesis involves treating a haloalkane with a metal alkoxide. Following are two reactions intended to give benzyl *tert*-butyl ether. One reaction gives the ether in good yield, the other does not. Which reaction gives the ether? What is the product of the other reaction, and how do you account for its formation?

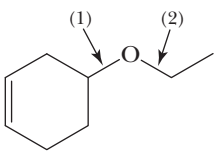
(a) 

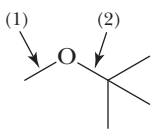


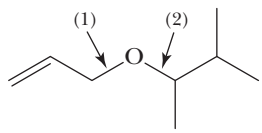
(b) 



7.46 The following ethers can, in principle, be synthesized by two different combinations of haloalkane or halocycloalkane and metal alkoxide. Show one combination that forms ether bond (1) and another that forms ether bond (2). Which combination gives the higher yield of ether?

(a) 

(b) 

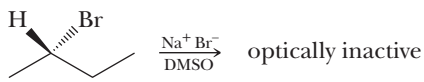
(c) 

7.47 Propose a mechanism for this reaction:

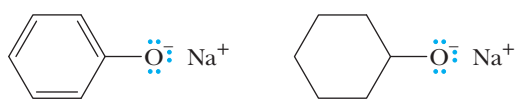

2-Chloroethanol Ethylene oxide

7.48 An OH group is a poor leaving group, and yet substitution occurs readily in the following reaction. Propose a mechanism for this reaction that shows how OH overcomes its limitation of being a poor leaving group.

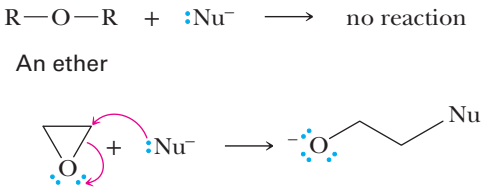
7.49 Explain why (*S*)-2-bromobutane becomes optically inactive when treated with sodium bromide in DMSO:


optically active optically inactive

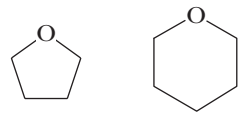
7.50 Explain why phenoxide is a much poorer nucleophile and weaker base than cyclohexoxide:


Sodium phenoxide Sodium cyclohexoxide

7.51 In ethers, each side of the oxygen is essentially an OR group and is thus a poor leaving group. Epoxides are three-membered ring ethers. Explain why an epoxide reacts readily with a nucleophile despite being an ether.



Would you expect the five-membered and six-membered ring ethers shown to react with nucleophiles the same way that epoxides react with nucleophiles? Why or why not?



GROUP LEARNING ACTIVITIES

7.52 Discuss and come up with examples of the following:

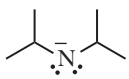
(a) a negatively charged reagent that is a weak base

(b) a negatively charged reagent that is a poor nucleophile

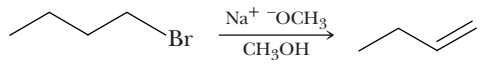
(c) aside from chloride, bromide, or iodide, a negatively charged reagent that is a good leaving group

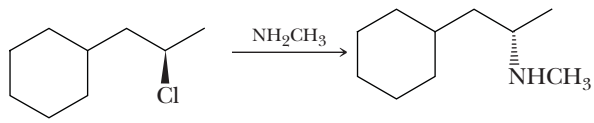
7.53 Discuss reasons why the following statements are true:

(a) although hexane is an aprotic solvent, it is a poor solvent for an S_N2 reaction

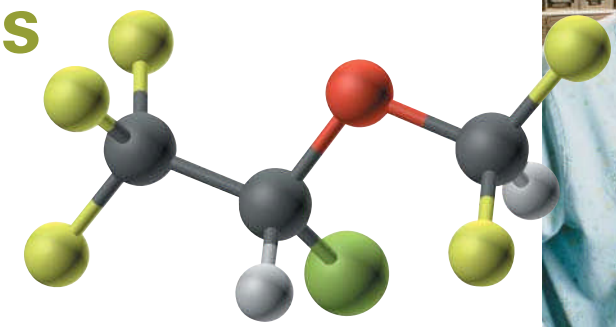
(b) $CH_3\ddot{N}H^-$, is a better nucleophile than $CH_3\ddot{O}:^-$, but  is better than 

7.54 Discuss ways that you could speed up the following reactions without changing the products formed.

(a) 

(b) 

Alcohols, Ethers, and Thiols



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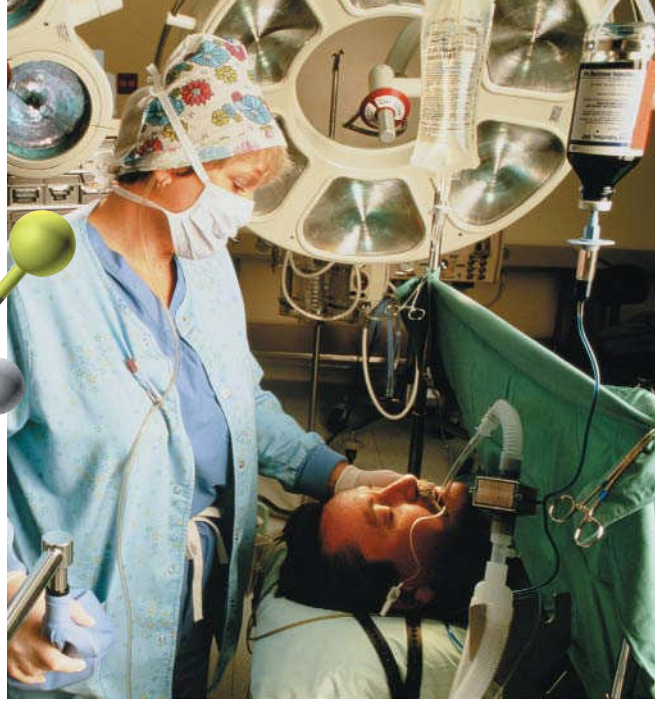
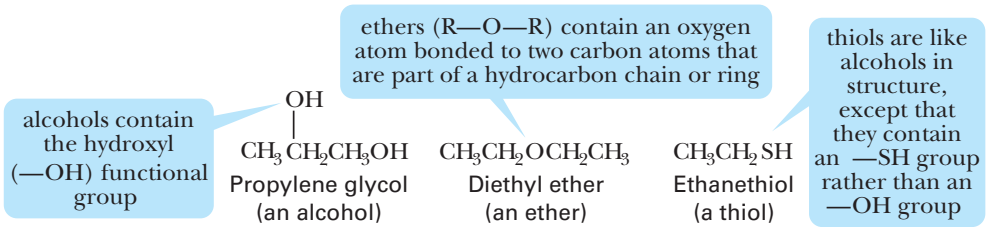


An anesthesiologist administers isoflurane to a patient before surgery. The discovery that inhaling ethers could make a patient insensitive to pain revolutionized the practice of medicine. Inset: A model of isoflurane, $CF_3CHClOCHF_2$, a halogenated ether widely used as an inhalation anesthetic in both human and veterinary medicine.

Alan Levenson/Stone/Getty Images

CONSIDER THE DE-ICING LIQUID (propylene glycol) that is sprayed onto an airplane in subfreezing weather, the sleep-inducing gas (diethyl ether) that revolutionized the field of general surgery in the 1800s, and the rotten egg smell (ethanethiol) added to liquified petroleum gas tanks (a.k.a. "propane" tanks) to indicate the presence of the gas. These three examples represent alcohols, ethers, and thiols, the three classes of compounds we will study in this chapter.



Alcohols, in particular, are very important in both laboratory and biochemical transformations of organic compounds. They can be converted into other types of compounds, such as

alkenes, haloalkanes, aldehydes, ketones, carboxylic acids, and esters. Not only can alcohols be converted to these compounds, but they also can be prepared from them. We already saw how alcohols can be prepared from alkenes (Section 5.3B) and haloalkanes (Section 7.4). Alcohols play a central role in the interconversion of organic functional groups and thus in our ability to synthesize life-saving and life-enhancing compounds.

8.1 What Are Alcohols?

A. Structure

The functional group of an **alcohol** is an —**OH (hydroxyl) group** bonded to an sp^3 hybridized carbon atom (Section 1.7A). The oxygen atom of an alcohol is also sp^3 hybridized. Two sp^3 hybrid orbitals of oxygen form sigma bonds to atoms of carbon and hydrogen. The other two sp^3 hybrid orbitals of oxygen each contain an unshared pair of electrons. Figure 8.1 shows a Lewis structure and ball-and-stick model of methanol, CH_3OH, the simplest alcohol.

Alcohol A compound containing an —OH (hydroxyl) group bonded to an sp^3 hybridized carbon.

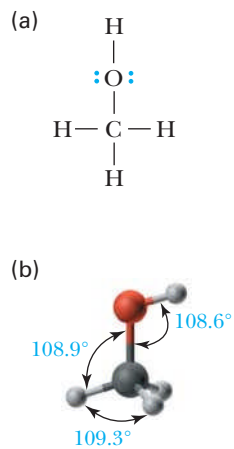


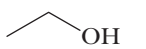
FIGURE 8.1 Methanol, CH_3OH. (a) Lewis structure and (b) ball-and-stick model. The measured H—O—C bond angle in methanol is 108.6°, very close to the tetrahedral angle of 109.5°.

B. Nomenclature

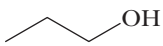
We derive the IUPAC names for alcohols in the same manner as those for alkanes, with the exception that the ending of the parent alkane is changed from *-e* to *-ol*. The ending *-ol* tells us that the compound is an alcohol.

1. Select, as the parent alkane, the longest chain of carbon atoms that contains the —OH, and number that chain from the end closer to the —OH group. In numbering the parent chain, the location of the —OH group takes precedence over alkyl groups and halogens.
2. Change the suffix of the parent alkane from *-e* to *-ol* (Section 3.5), and use a number to show the location of the —OH group. For cyclic alcohols, numbering begins at the carbon bearing the —OH group.
3. Name and number substituents and list them in alphabetical order.

To derive common names for alcohols, we name the alkyl group bonded to —OH and then add the word *alcohol*. Following are the IUPAC names and, in parentheses, the common names of eight low-molecular-weight alcohols:

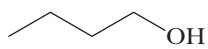


Ethanol
(Ethyl alcohol)

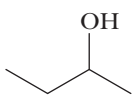


1-Propanol
(Propyl alcohol)

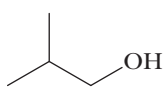
2-Propanol
(Isopropyl alcohol)



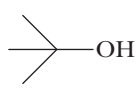
1-Butanol
(Butyl alcohol)



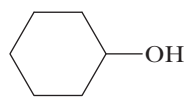
2-Butanol
(*sec*-Butyl alcohol)



2-Methyl-1-propanol
(Isobutyl alcohol)



2-Methyl-2-propanol
(*tert*-Butyl alcohol)



Cyclohexanol
(Cyclohexyl alcohol)

We classify alcohols as **primary (1°)**, **secondary (2°)**, or **tertiary (3°)**, depending on whether the —OH group is on a primary, secondary, or tertiary carbon (Section 1.7A).

In the IUPAC system, a compound containing two hydroxyl groups is named as a **diol**, one containing three hydroxyl groups is named as a **triol**, and so on. In IUPAC names for diols, triols, and so on, the final *-e* of the parent alkane name is retained, as for example, in 1,2-ethanediol. Compounds containing two hydroxyl groups on different carbons are often

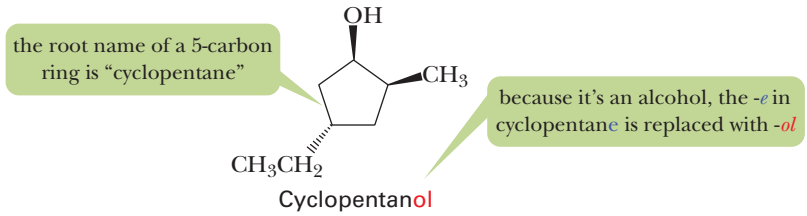
Charles D. Winters

Ethylene glycol is a polar molecule and dissolves readily in water, a polar solvent.

Name Cyclic Alcohols

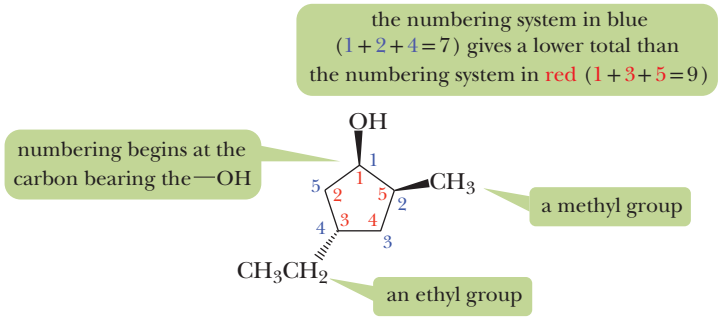
HOW TO 8.1

(a) First, determine the root name of the cycloalkane, and replace the suffix *-e* with *-ol*.

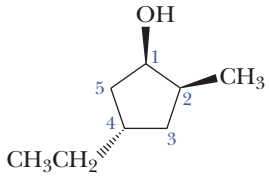


Cyclopentanol

(b) Name and number the substituents. Numbering begins at the carbon bearing the —OH group and proceeds in the direction that gives the lowest *total* for all substituents.

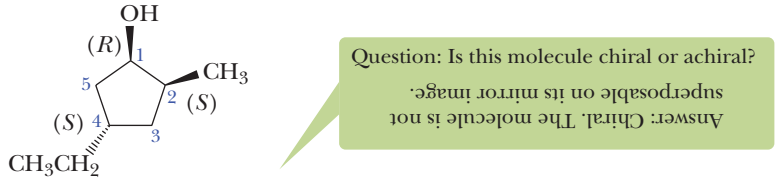


(c) Place substituents in alphabetical order preceded by its position on the ring. Position 1 for the —OH group is assumed.



4-Ethyl-2-methylcyclopentanol

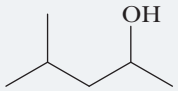
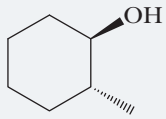
(d) Don't forget to indicate stereochemistry.



(1*R*,2*S*,4*S*)-4-Ethyl-2-methylcyclopentanol

EXAMPLE 8.1

Write the IUPAC name for each alcohol:

(a) $CH_3(CH_2)_6CH_2OH$ **(b)**  **(c)**  **(d)** $(CH_3CH_2CH_2)_2CHCH_2OH$

STRATEGY

First look for the longest chain of carbons that contains the —OH group. This will allow you to determine the root name. Then identify the atoms or groups of atoms that are not part of that chain of carbons. These are your substituents.

SOLUTION

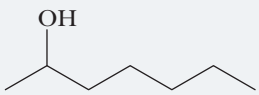
(a) 1-Octanol **(b)** 4-Methyl-2-pentanol **(c)** *trans*-2-Methylcyclohexanol or (1*R*,2*R*)-2-Methylcyclohexanol **(d)** 2-propyl-1-pentanol

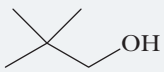
this name does not specify configuration and would not allow one to know which enantiomer of this chiral compound is being referenced

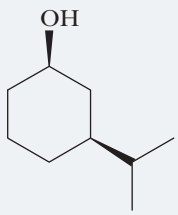
See problems 8.14, 8.15, 8.17

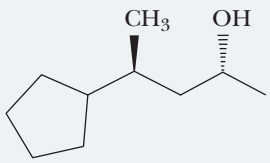
PROBLEM 8.1

Write the IUPAC name for each alcohol:

(a) 

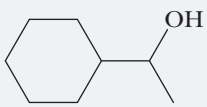
(b) 

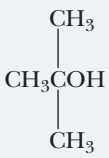
(c) 

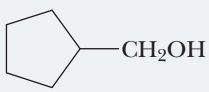
(d) 

EXAMPLE 8.2

Classify each alcohol as primary, secondary, or tertiary:

(a) 

(b) 

(c) 

STRATEGY

Determine how many carbons are bonded to the carbon bonded to the —OH group (1 carbon = 1°, 2 carbons = 2°, and 3 carbons = 3°).

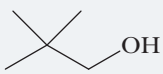
SOLUTION

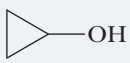
(a) Secondary (2°) **(b)** Tertiary (3°) **(c)** Primary (1°)

See problem 8.13

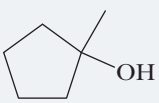
PROBLEM 8.2

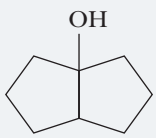
Classify each alcohol as primary, secondary, or tertiary:

(a) 

(b) 

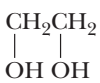
(c) $CH_2{=}CHCH_2OH$

(d) 

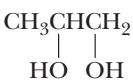
(e) 

referred to as **glycols** Ethylene glycol and propylene glycol are synthesized from ethylene and propylene, respectively—hence their common names:

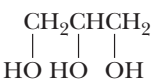
Glycols A compound with two hydroxyl (—OH) groups on different carbons.



1,2-Ethanediol
(Ethylene glycol)



1,2-Propanediol
(Propylene glycol)



1,2,3-Propanetriol
(Glycerol, Glycerin)

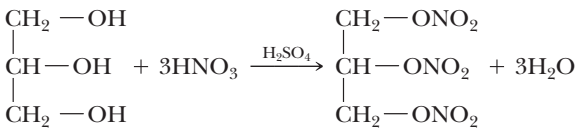
We often refer to compounds containing —OH and C═C groups as unsaturated alcohols. To name an unsaturated alcohol,

1. Number the parent alkane so as to give the —OH group the lowest possible number.
2. Show the double bond by changing the infix of the parent alkane from *-an-* to *-en-* (Section 3.5), and show the alcohol by changing the suffix of the parent alkane from *-e* to *-ol*.
3. Use numbers to show the location of both the carbon–carbon double bond and the hydroxyl group. Recall that the hydroxyl group takes precedence when numbering the parent chain.

Chemical Connections 8A

NITROGLYCERIN: AN EXPLOSIVE AND A DRUG

In 1847, Ascanio Sobrero (1812–1888) discovered that 1,2,3-propanetriol, more commonly named glycerin, reacts with nitric acid in the presence of sulfuric acid to give a pale yellow, oily liquid called nitroglycerin:



1,2,3-Propanetriol (Glycerol, Glycerin) | 1,2,3-Propanetriol trinitrate (Nitroglycerin)

Sobrero also discovered the explosive properties of the compound: When he heated a small quantity of it, it exploded! Soon, nitroglycerin became widely used for blasting in the construction of canals, tunnels, roads, and mines and, of course, for warfare.

One problem with the use of nitroglycerin was soon recognized: It was difficult to handle safely, and accidental explosions occurred frequently. The Swedish chemist Alfred Nobel (1833–1896) solved the problem: He discovered that a claylike substance called diatomaceous earth absorbs nitroglycerin so that it will not explode without a fuse. He gave the name *dynamite* to this mixture of nitroglycerin, diatomaceous earth, and sodium carbonate.

Surprising as it may seem, nitroglycerin is used in medicine to treat angina pectoris, the symptoms of which are sharp chest pains caused by a reduced flow of blood in the coronary artery. Nitroglycerin, which is available in liquid (diluted with alcohol to render it nonexplosive), tablet, or paste form, relaxes the smooth muscles of blood vessels, causing dilation of the coronary artery. This dilation, in turn, allows more blood to reach the heart.

© Bettmann/Corbis

The fortune of Alfred Nobel, 1833–1896, built on the manufacture of dynamite, now funds the Nobel Prizes.

When Nobel became ill with heart disease, his physicians advised him to take nitroglycerin to relieve his chest pains. He refused, saying he could not understand how the explosive could relieve chest pains. It took science more than 100 years to find the answer. We now know that it is nitric oxide, NO, derived from the nitro groups of nitroglycerin, that relieves the pain.

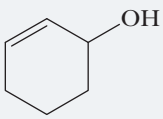
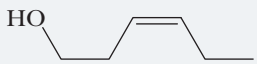
Question

Classify each hydroxyl group in glycerol as either 1°, 2°, or 3°.

EXAMPLE 8.3

Write the IUPAC name for each alcohol:

(a) $CH_2{=}CHCH_2OH$ (b) 

(c)  (d) 

STRATEGY

First look for the longest chain of carbons. This will allow you to determine the root name. If the alcohol is unsaturated, the name will follow the general form #-alken-#-ol. If there are two —OH groups, name the compound as an #,#-alkanediol if it is saturated or as an #-alken-#,#-diol if it is unsaturated.

SOLUTION

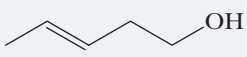
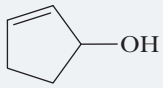
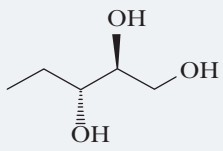
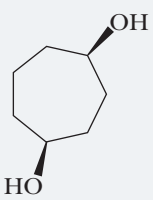
(a) 2-Propen-1-ol. Its common name is allyl alcohol.
(b) 2,2-Dimethyl-1,4-butanediol.
(c) 2-Cyclohexenol.
(d) *cis*-3-Hexen-1-ol. This unsaturated alcohol is sometimes called leaf alcohol because of its occurrence in leaves of fragrant plants, including trees and shrubs.

in this cyclic alcohol, the location of the —OH group is assumed to be at C-1

See problems 8.14, 8.15, 8.17

PROBLEM 8.3

Write the IUPAC name for each alcohol:

(a)  (b)  (c)  (d) 

C. Physical Properties

The most important physical property of alcohols is the polarity of their —OH groups. Because of the large difference in electronegativity (Table 1.5) between oxygen and carbon (3.5 – 2.5 = 1.0) and between oxygen and hydrogen (3.5 – 2.1 = 1.4), both the C—O and O—H bonds of an alcohol are polar covalent, and alcohols are polar molecules, as illustrated in Figure 8.2 for methanol.

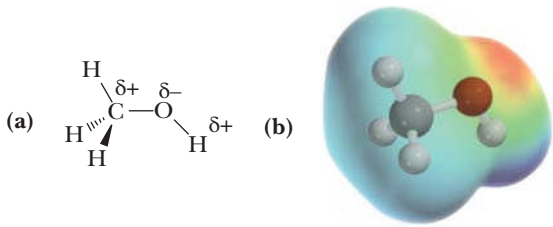


FIGURE 8.2 Polarity of the C—O—H bond in methanol. (a) There are partial positive charges on carbon and hydrogen and a partial negative charge on oxygen. (b) An electron density map showing the partial negative charge (in red) around oxygen and a partial positive charge (in blue) around hydrogen of the —OH group.

Table 8.1 lists the boiling points and solubilities in water for five groups of alcohols and alkanes of similar molecular weight. Notice that, of the compounds compared in each group, the alcohol has the higher boiling point and is the more soluble in water.

Alcohols have higher boiling points than alkanes of similar molecular weight, because alcohols are polar molecules and can associate in the liquid state by a type of dipole–dipole intermolecular attraction called **hydrogen bonding** (Figure 8.3). The strength of hydrogen bonding between alcohol molecules is approximately 8.4 to 21 kJ/mol (2 to 5 kcal/mol). For comparison, the strength of the O—H covalent bond in an alcohol molecule is approximately 460 kJ/mol (110 kcal/ mol). As we see by comparing these numbers, an O—H hydrogen bond is considerably weaker than an O—H covalent bond. Nonetheless, it is sufficient to have a dramatic effect on the physical properties of alcohols.

Hydrogen bonding The attractive force between a partial positive charge on hydrogen and partial negative charge on a nearby oxygen, nitrogen, or fluorine atom.

Because of hydrogen bonding between alcohol molecules in the liquid state, extra energy is required to separate each hydrogen-bonded alcohol molecule from its neighbors—hence the relatively high boiling points of alcohols compared with those of alkanes. The presence of additional hydroxyl groups in a molecule further increases the extent of hydrogen bonding, as can be seen by comparing the boiling points of 1-pentanol (138 °C) and 1,4-butanediol (230 °C), both of which have approximately the same molecular weight.

Because of increased dispersion forces (Section 3.8B) between larger molecules, boiling points of all types of compounds, including alcohols, increase with increasing

TABLE 8.1 Boiling Points and Solubilities in Water of Alcohols and Alkanes Grouped by Similar Molecular Weight

Structural Formula	Name	Molecular Weight	Boiling Point (°C)	Solubility in water
CH_3OH	methanol	32	65	infinite
CH_3CH_3	ethane	30	–89	insoluble
CH_3CH_2OH	ethanol	46	78	infinite
$CH_3CH_2CH_3$	propane	44	–42	insoluble
$CH_3CH_2CH_2OH$	1-propanol	60	97	infinite
$CH_3CH_2CH_2CH_3$	butane	58	0	insoluble
$CH_3CH_2CH_2CH_2OH$	1-butanol	74	117	8 g /100 g
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	insoluble
$CH_3CH_2CH_2CH_2CH_2OH$	1-pentanol	88	138	2.3 g /100 g
$HOCH_2CH_2CH_2CH_2OH$	1,4-butanediol	90	230	infinite
$CH_3CH_2CH_2CH_2CH_2CH_3$	hexane	86	69	insoluble

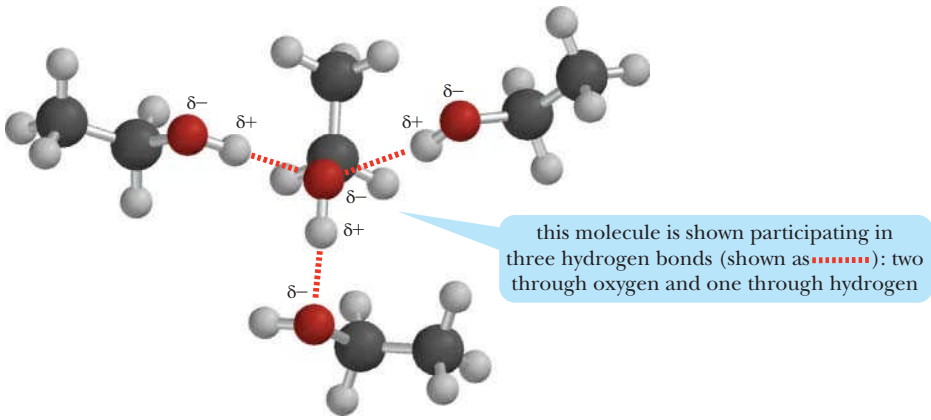


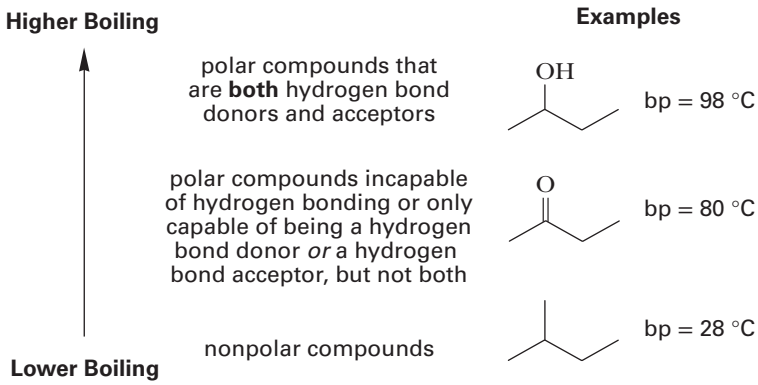
FIGURE 8.3 The association of ethanol molecules in the liquid state. Each O—H can participate in up to three hydrogen bonds (one through hydrogen and two through oxygen).

HOW TO 8.2

Predict Relative Boiling Points of Compounds of Similar Molecular Weight

(a) Look for features that make a compound's boiling point higher than another's such as greater polarity, the ability to form hydrogen bonds with that compound's molecules (true for compounds containing N—H or O—H bonds), and greater surface area.

(b) Boiling will typically follow the trend:



molecular weight. (Compare, for example, the boiling points of ethanol, 1-propanol, 1-butanol, and 1-pentanol.)

Alcohols are much more soluble in water than are alkanes, alkenes, and alkynes of comparable molecular weight. Their increased solubility is due to hydrogen bonding between alcohol molecules and water. Methanol, ethanol, and 1-propanol are soluble in water in all proportions. As molecular weight increases, the physical properties of alcohols become more like those of hydrocarbons with comparable molecular weight. Alcohols with higher molecular weight are much less soluble in water because of the increase in size of the hydrocarbon portion of their molecules.

8.2 What Are the Characteristic Reactions of Alcohols?

In this section, we study the acidity and basicity of alcohols, their dehydration to alkenes, their conversion to haloalkanes, and their oxidation to aldehydes, ketones, or carboxylic acids.

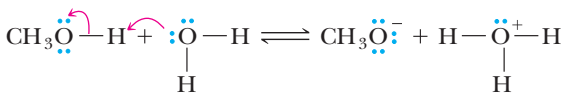
TABLE 8.2 pK_a Values for Selected Alcohols in Dilute Aqueous Solution*

Compound	Structural Formula	pK_a	
hydrogen chloride	HCl	–7	Stronger acid
acetic acid	CH_3COOH	4.8	
methanol	CH_3OH	15.5	
water	H_2O	15.7	
ethanol	CH_3CH_2OH	15.9	
2-propanol	$(CH_3)_2CHOH$	17	Weaker acid
2-methyl-2-propanol	$(CH_3)_3COH$	18	

*Also given for comparison are pK_a values for water, acetic acid, and hydrogen chloride.

A. Acidity of Alcohols

Alcohols have about the same pK_a values as water (15.7), which means that aqueous solutions of alcohols have about the same pH as that of pure water. The pK_a of methanol, for example, is 15.5:



(pK_a = 15.5) (pK_a = 15.7)

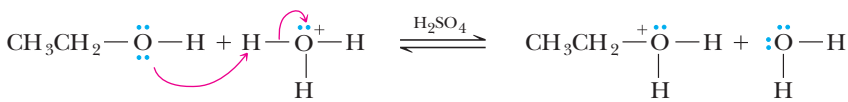
$$K_a = \frac{[CH_3O^-][H_3O^+]}{[CH_3OH]} = 3.2 \times 10^{-16}$$

$$pK_a = 15.5$$

Table 8.2 gives the acid ionization constants for several low-molecular-weight alcohols. Methanol and ethanol are about as acidic as water. Higher-molecular-weight, water-soluble alcohols are slightly weaker acids than water. Even though alcohols have some slight acidity, they are not strong enough acids to react with weak bases such as sodium bicarbonate or sodium carbonate. (At this point, it would be worthwhile to review Section 2.4 and the discussion of the position of equilibrium in acid–base reactions.) Note that, although acetic acid is a "weak acid" compared with acids such as HCl, it is still 10^{10} times stronger as an acid than alcohols are.

B. Basicity of Alcohols

In the presence of strong acids, the oxygen atom of an alcohol is a weak base and reacts with an acid by proton transfer to form an oxonium ion:



Ethanol — Hydronium ion (pK_a –1.7) — Ethyloxonium ion (pK_a –2.4)

Thus, alcohols can function as both weak acids and weak bases.

C. Reaction with Active Metals

Like water, alcohols react with Li, Na, K, Mg, and other **active metals** to liberate hydrogen and to form metal alkoxides. In the following oxidation–reduction reaction, Na is oxidized to Na^+ and H^+ is reduced to H_2:

$$2\ CH_3OH + 2\ Na \longrightarrow \underset{\text{Sodium methoxide}}{2\ CH_3O^-Na^+} + H_2$$

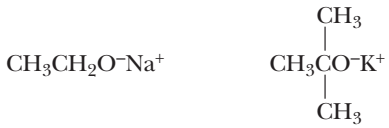
Charles D. Winters

Methanol reacts with sodium metal to give sodium methoxide along with the evolution of hydrogen gas.

Active metal A metal that readily loses an electron to form a cation.

To name a metal alkoxide, name the cation first, followed by the name of the anion. The name of an alkoxide ion is derived from a prefix showing the number of carbon atoms and their arrangement (*meth-*, *eth-*, *isoprop-*, tert-*but-*, and so on) followed by the suffix *-oxide*.

Alkoxide ions are somewhat stronger bases than is the hydroxide ion. In addition to sodium methoxide, the following metal salts of alcohols are commonly used in organic reactions requiring a strong base in a nonaqueous solvent; sodium ethoxide in ethanol and potassium *tert*-butoxide in 2-methyl-2-propanol (*tert*-butyl alcohol):



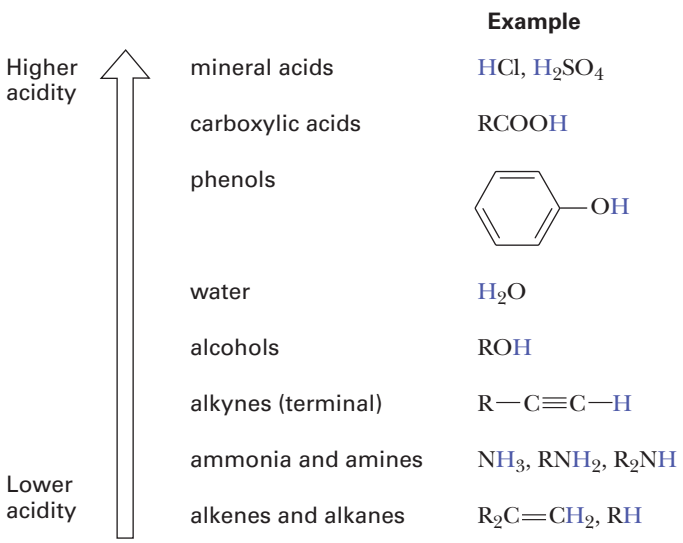
Sodium ethoxide Potassium *tert*-butoxide

As we saw in Chapter 7, alkoxide ions can also be used as nucleophiles in substitution reactions.

Predict the Position of Equilibrium of an Acid–Base Reaction

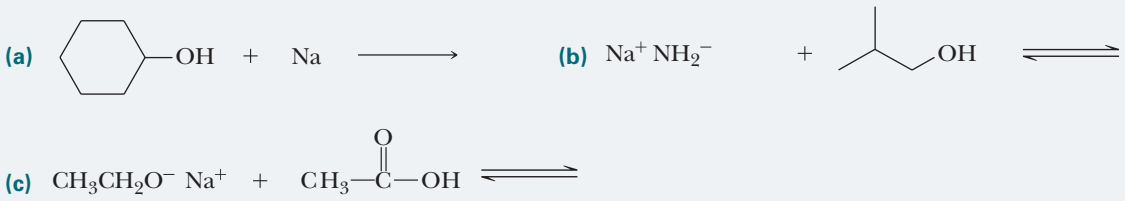
HOW TO 8.3

See How To 2.2 for guidelines on predicting relative acidities. The following are relative acidities of common types of compounds encountered in organic chemistry.



EXAMPLE 8.4

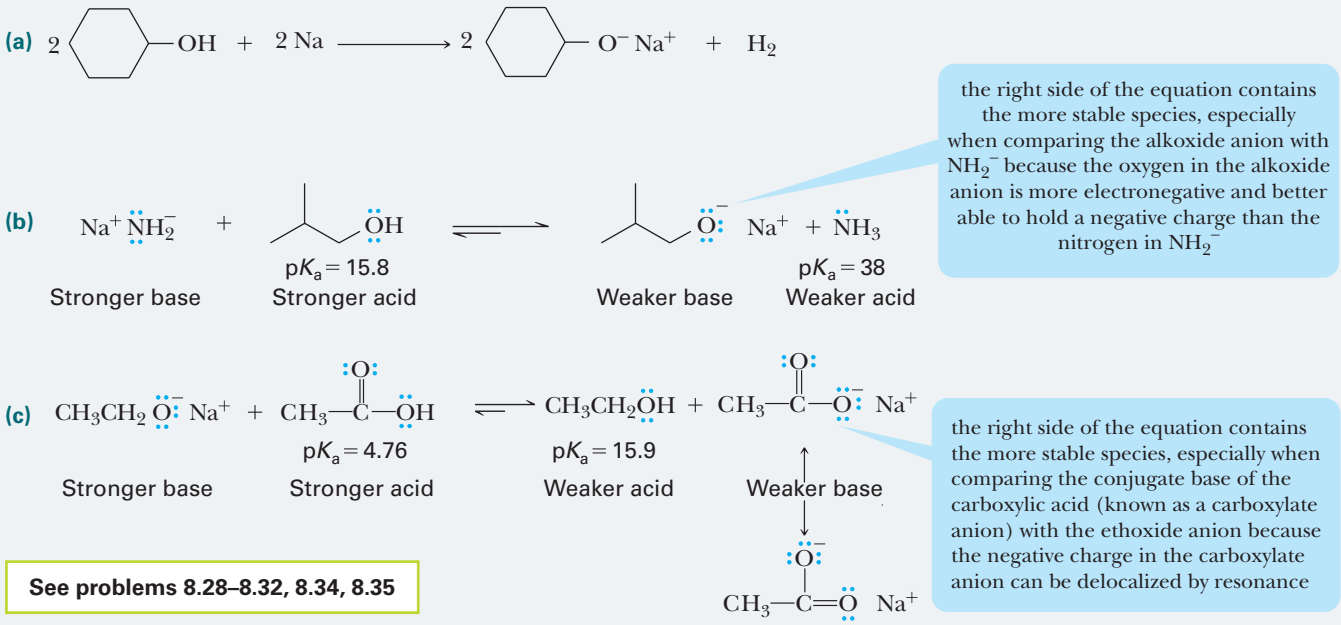
Write balanced equations for the following reactions. If the reaction is an acid–base reaction, predict its position of equilibrium.



STRATEGY

First determine what type of reaction is occurring. When elemental sodium is used, an oxidation–reduction reaction takes place, producing a sodium alkoxide and hydrogen gas. In acid–base reactions, the position of the equilibrium resides on the side with the weaker acid and weaker base (i.e., the more stable species).

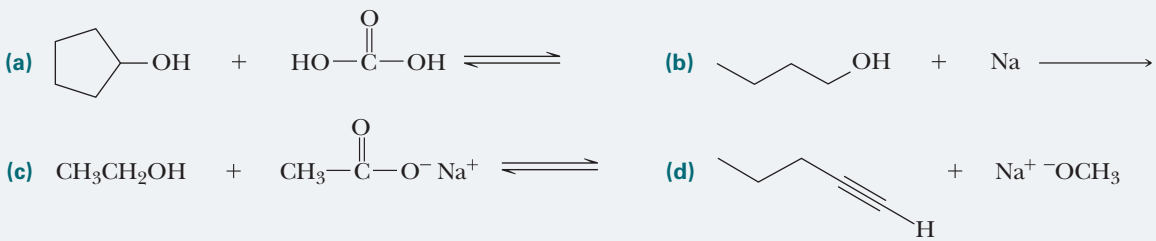
SOLUTION



See problems 8.28–8.32, 8.34, 8.35

PROBLEM 8.4

Write balanced equations for the following reactions. If the reaction is an acid–base reaction, predict its position of equilibrium.

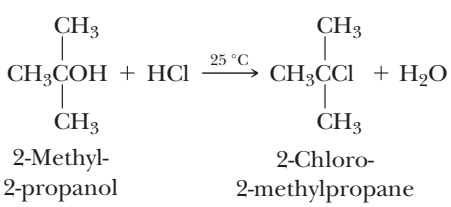


D. Conversion to Haloalkanes

The conversion of an alcohol to an alkyl halide involves substituting halogen for —OH at a saturated carbon. The most common reagents for this conversion are the halogen acids and $SOCl_2$.

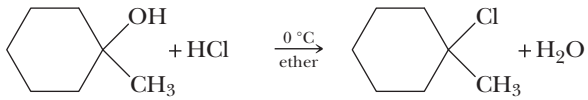
Reaction with HCl, HBr, and HI

Water-soluble tertiary alcohols react very rapidly with HCl, HBr, and HI. Mixing a tertiary alcohol with concentrated hydrochloric acid for a few minutes at room temperature converts the alcohol to a water-insoluble chloroalkane that separates from the aqueous layer.



Low-molecular-weight, water-soluble primary and secondary alcohols do not react under these conditions.

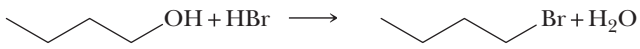
Water-insoluble tertiary alcohols are converted to tertiary halides by bubbling gaseous HX through a solution of the alcohol dissolved in diethyl ether or tetrahydrofuran (THF):



1-Methylcyclohexanol — 1-Chloro-1-methylcyclohexane

Water-insoluble primary and secondary alcohols react only slowly under these conditions.

Primary and secondary alcohols are converted to bromoalkanes and iodoalkanes by treatment with concentrated hydrobromic and hydroiodic acids. For example, heating 1-butanol with concentrated HBr gives 1-bromobutane:



1-Butanol — 1-Bromobutane (Butyl bromide)

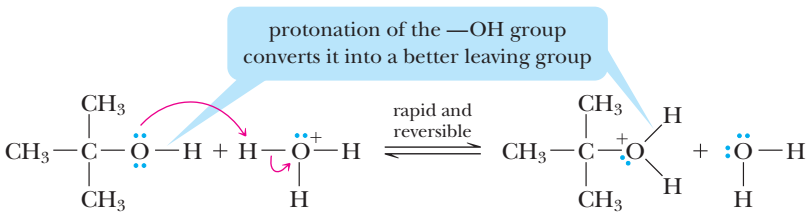
On the basis of observations of the relative ease of reaction of alcohols with HX (3° > 2° > 1°), it has been proposed that the conversion of tertiary and secondary alcohols to haloalkanes by concentrated HX occurs by an S_N1 mechanism (Section 7.4) and involves the formation of a carbocation intermediate. *Note:* Recall that secondary carbocations are subject to rearrangement to more stable tertiary carbocations (Section 5.4).

Mechanism

Reaction of a Tertiary Alcohol with HCl: An S_N1 Reaction

STEP 1: *Add a proton.*

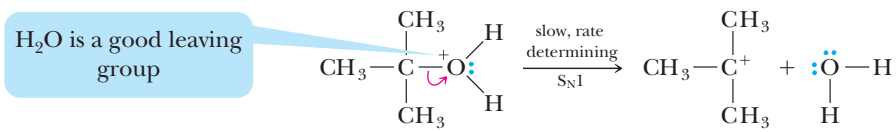
Rapid and reversible proton transfer from the acid to the OH group gives an oxonium ion. The result of this proton transfer is to convert the leaving group from OH^-, a poor leaving group, to H_2O, a better leaving group:



2-Methyl-2-propanol (*tert*-Butyl alcohol) — An oxonium ion

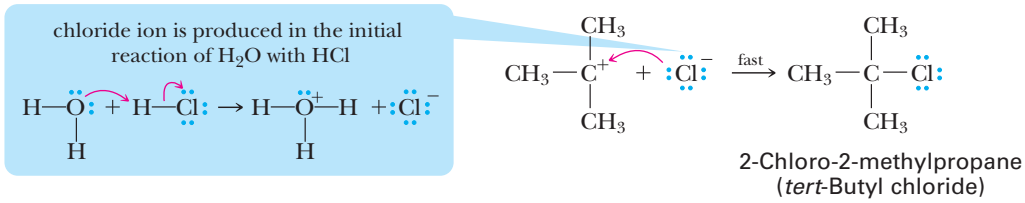
STEP 2: *Break a bond to form a stable molecule or ion.*

Loss of water from the oxonium ion gives a 3° carbocation intermediate:



An oxonium ion — A 3° carbocation intermediate

STEP 3: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*
Reaction of the 3° carbocation intermediate (an electrophile) with chloride ion (a nucleophile) gives the product:

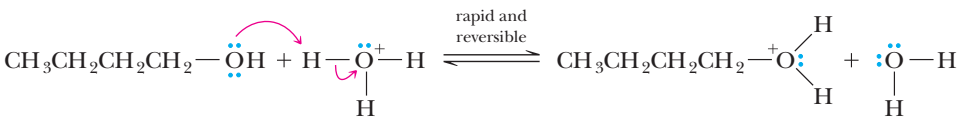


Primary alcohols react with HX by an S_N2 mechanism. In the rate-determining step, the halide ion displaces H_2O from the carbon bearing the oxonium ion. The displacement of H_2O and the formation of the C—X bond are simultaneous.

Mechanism

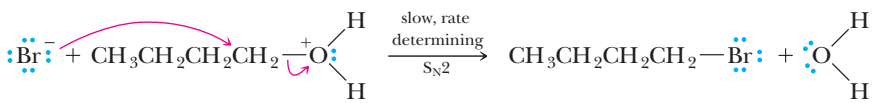
Reaction of a Primary Alcohol with HBr: An S_N2 Reaction

STEP 1: *Add a proton.*
Rapid and reversible proton transfer to the OH group which converts the leaving group from OH^-, a poor leaving group, to H_2O, a better leaving group:



An oxonium ion

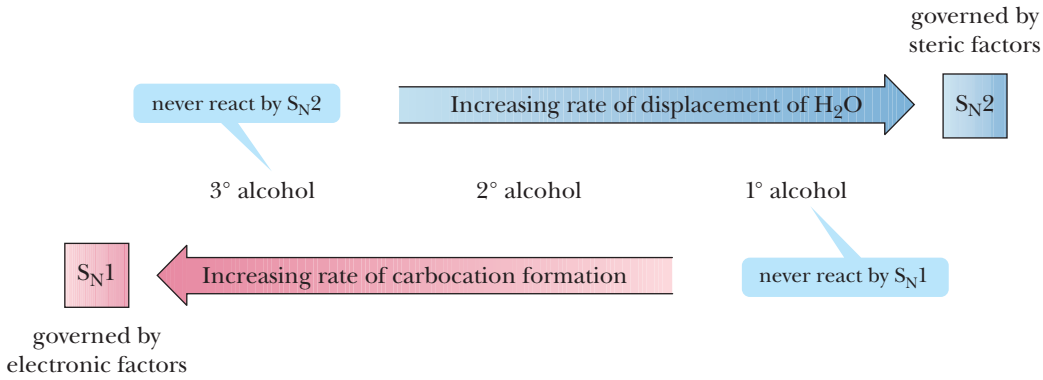
STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond and break a bond to form a stable molecule or ion.*
The nucleophilic displacement of H_2O by Br^- gives the bromoalkane:



Why do tertiary alcohols react with HX by formation of carbocation intermediates, whereas primary alcohols react by direct displacement of —OH (more accurately, by displacement of $—OH_2^+$)? The answer is a combination of the same two factors involved in nucleophilic substitution reactions of haloalkanes (Section 7.5B):

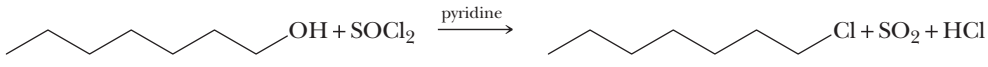
1. *Electronic factors* Tertiary carbocations are the most stable (require the lowest activation energy for their formation), whereas primary carbocations are the least stable (require the highest activation energy for their formation). Therefore, tertiary alcohols are most likely to react by carbocation formation; secondary alcohols are intermediate, and primary alcohols rarely, if ever, react by carbocation formation.

2. *Steric factors* To form a new carbon–halogen bond, halide ion must approach the substitution center and begin to form a new covalent bond to it. If we compare the ease of approach to the substitution center of a primary oxonium ion with that of a tertiary oxonium ion, we see that approach is considerably easier in the case of a primary oxonium ion. Two hydrogen atoms and one alkyl group screen the back side of the substitution center of a primary oxonium ion, whereas three alkyl groups screen the back side of the substitution center of a tertiary oxonium ion.



Reaction with Thionyl Chloride

The most widely used reagent for the conversion of primary and secondary alcohols to alkyl chlorides is thionyl chloride, $SOCl_2$. The by-products of this nucleophilic substitution reaction are HCl and SO_2, both given off as gases. Often, an organic base such as pyridine (Section 10.1) is added to react with and neutralize the HCl by-product:

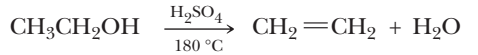


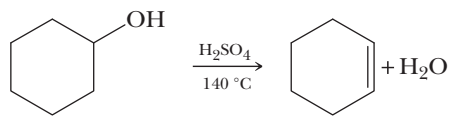
1-Heptanol — Thionyl chloride — 1-Chloroheptane

E. Acid-Catalyzed Dehydration to Alkenes

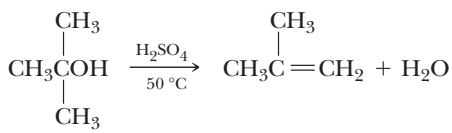
Dehydration Elimination of a molecule of water from a compound.

An alcohol can be converted to an alkene by **dehydration**—that is, by the elimination of a molecule of water from adjacent carbon atoms. In the laboratory, the dehydration of an alcohol is most often brought about by heating it with either 85% phosphoric acid or concentrated sulfuric acid. Primary alcohols are the most difficult to dehydrate and generally require heating in concentrated sulfuric acid at temperatures as high as 180°C. Secondary alcohols undergo acid-catalyzed dehydration at somewhat lower temperatures. The acid-catalyzed dehydration of tertiary alcohols often requires temperatures only slightly above room temperature:





Cyclohexanol — Cyclohexene



2-Methyl-2-propanol (*tert*-Butyl alcohol) — 2-Methylpropene (Isobutylene)

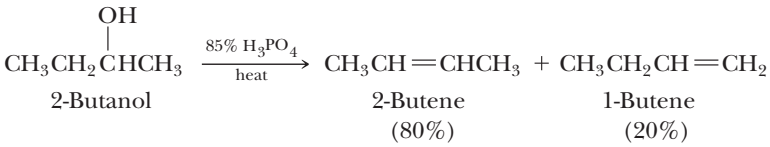
Thus, the ease of acid-catalyzed dehydration of alcohols occurs in this order:

1° alcohol < 2° alcohol < 3° alcohol

Ease of dehydration of alcohols

When isomeric alkenes are obtained in the acid-catalyzed dehydration of an alcohol, the more stable alkene (the one with the greater number of substituents on the double

bond; see Section 5.3B) generally predominates; that is, the acid-catalyzed dehydration of alcohols follows Zaitsev's rule (Section 7.7):



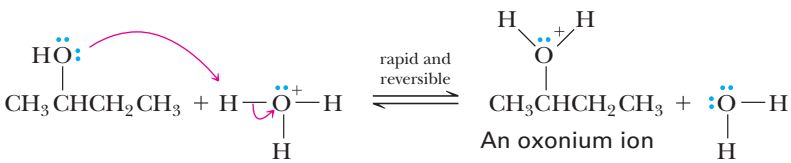
On the basis of the relative ease of dehydration of alcohols (3° > 2° > 1°), chemists propose a three-step mechanism for the acid-catalyzed dehydration of secondary and tertiary alcohols. This mechanism involves the formation of a carbocation intermediate in the rate-determining step and therefore is an E1 mechanism.

Mechanism

Acid-Catalyzed Dehydration of 2-Butanol: An E1 Mechanism

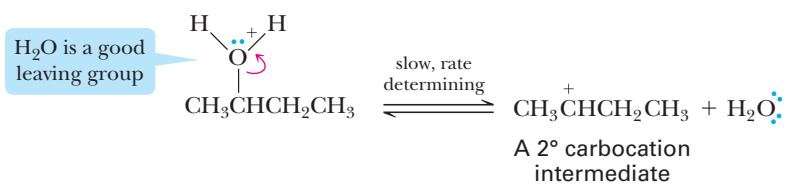
STEP 1: *Add a proton.*

Proton transfer from H_3O^+ to the OH group of the alcohol gives an oxonium ion. A result of this step is to convert OH^-, a poor leaving group, into H_2O, a better leaving group:



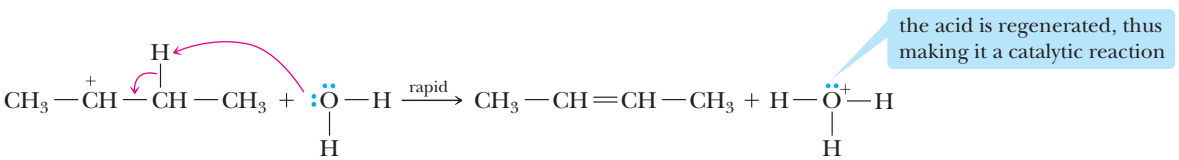
STEP 2: *Break a bond to form a stable molecule or ion.*

Breaking of the C—O bond gives a 2° carbocation intermediate and H_2O:



STEP 3: *Take away a proton.*

Proton transfer from the carbon adjacent to the positively charged carbon to H_2O gives the alkene and regenerates the catalyst. The sigma electrons of a C—H bond become the pi electrons of the carbon–carbon double bond:



Because the rate-determining step in the acid-catalyzed dehydration of secondary and tertiary alcohols is the formation of a carbocation intermediate, the relative ease of dehydration of these alcohols parallels the ease of formation of carbocations.

Primary alcohols react by the following two-step mechanism, in which Step 2 is the rate-determining step.

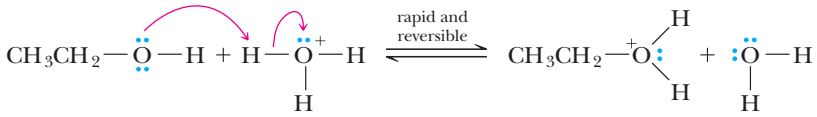
In Section 5.3B, we discussed the acid-catalyzed hydration of alkenes to give alcohols. In the current section, we discussed the acid-catalyzed dehydration of alcohols to give alkenes.

Mechanism

Acid-Catalyzed Dehydration of a Primary Alcohol: An E2 Mechanism

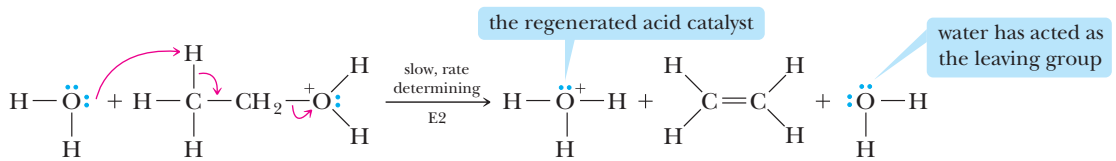
STEP 1: *Add a proton.*

Proton transfer from H_3O^+ to the OH group of the alcohol gives an oxonium ion:

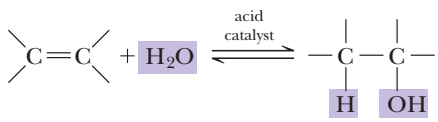


STEP 2: *Take a proton away and break a bond to form a stable molecule or ion.*

Simultaneous proton transfer to solvent and loss of H_2O gives the alkene:



In fact, hydration–dehydration reactions are reversible. Alkene hydration and alcohol dehydration are competing reactions, and the following equilibrium exists:

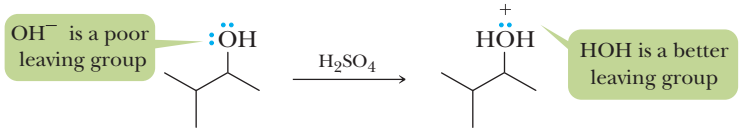


An alkene An alcohol

How, then, do we control which product will predominate? Recall that LeChâtelier's principle states that a system in equilibrium will respond to a stress in the equilibrium by counteracting that stress. This response allows us to control these two reactions to give the desired product. Large amounts of water (achieved with the use of dilute aqueous acid) favor alcohol formation, whereas a scarcity of water (achieved with the use of concentrated acid) or experimental conditions by which water is removed (for example, heating the reaction mixture above 100°C) favor alkene formation. Thus, depending on the experimental conditions, it is possible to use the hydration–dehydration equilibrium to prepare either alcohols or alkenes, each in high yields.

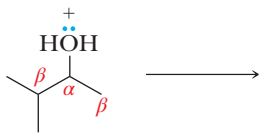
HOW TO 8.4 Complete a Dehydration Reaction

(a) A dehydration reaction is very similar to a dehydrohalogenation reaction (Section 7.7) except that the hydroxyl group must be protonated to generate a better leaving group.

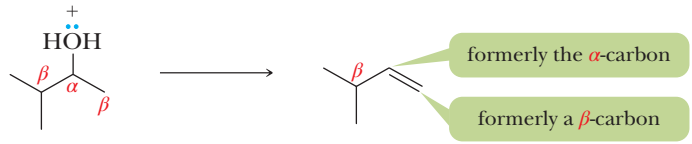


(b) Label the carbon bonded to the leaving group as "α" (alpha).

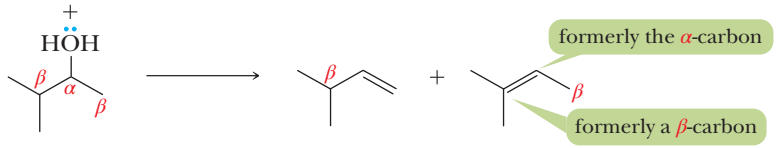
(c) Label any carbon bonded to the α-carbon as "β" (beta). *Note*: Only do so if the β-carbon is bonded to a hydrogen atom.



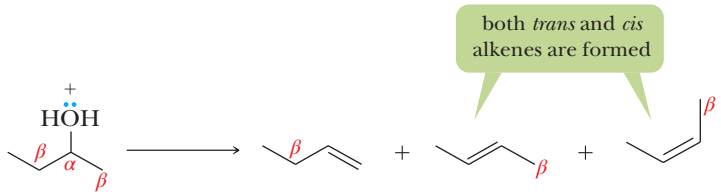
(d) Remove the leaving group (H_2O) and β-hydrogen from the molecule and place a new double bond between the α and β carbons. This forms a dehydration product.



(e) Repeat step (d) above for any other β-carbons to form a different dehydration product.

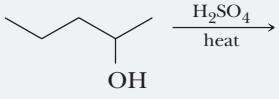


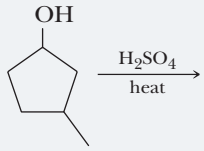
(f) When forming an alkene by E1 elimination, consider the fact that both *cis* and *trans* isomers of the alkene are possible.

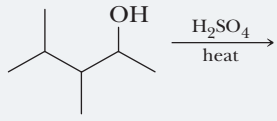


EXAMPLE 8.5

For each of the following alcohols, draw structural formulas for the alkenes that form upon acid-catalyzed dehydration, and predict which alkene is the major product from each alcohol. Be aware that rearrangements may occur because carbocations are formed in the reactions.

(a) 

(b) 

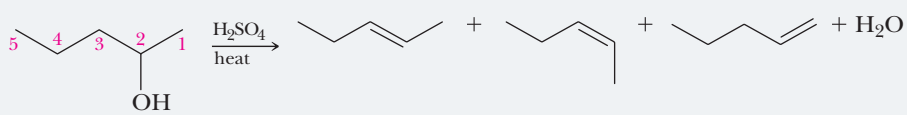
(c) 

STRATEGY

Label the carbon bonded to the —OH group as α. This is where the carbocation will form in the mechanism of the reaction. Consider whether a rearrangement (Section 5.4) will occur, and if so, relabel the new carbocation as α. Then label any carbons next to the α-carbon as β. If the β-carbon is bonded to at least one hydrogen, remove that hydrogen and the —OH and draw a C—C double bond between the α- and β-carbons. Start over and repeat this process for any other β-carbons that meet this criteria. Each time you are able to do this will result in an elimination product.

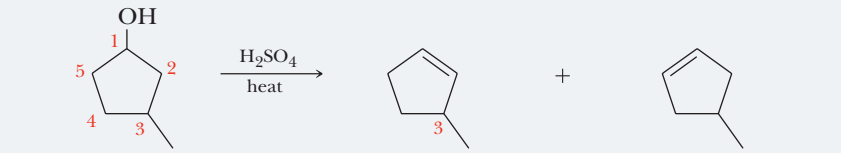
SOLUTION

(a) The elimination of H_2O from carbons 2 and 3 gives 2-pentene, which can form as *cis–trans* isomers; the elimination of H_2O from carbons 1 and 2 gives 1-pentene. *trans*-2-Pentene, with two alkyl groups (an ethyl and a methyl) on the double bond and with *trans* being more stable than *cis* (Section 5.6), is the major product. 1-Pentene, with only one alkyl group (a propyl group) on the double bond, is a minor product:



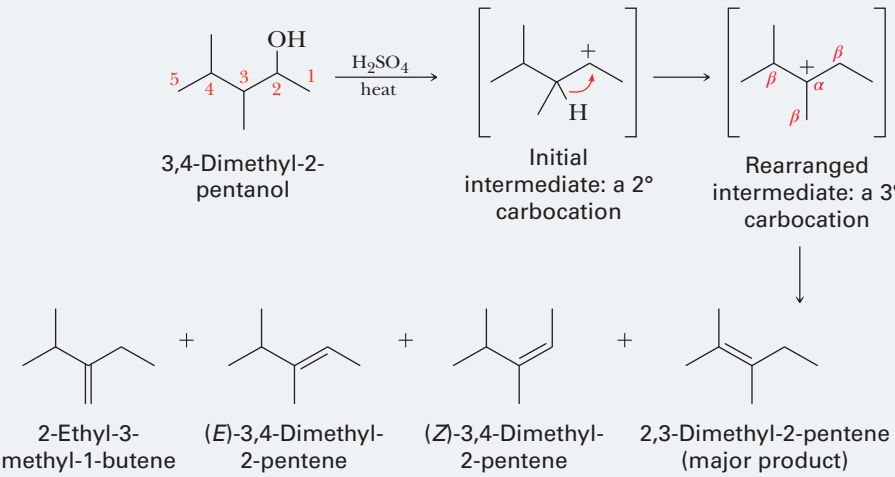
2-Pentanol — *trans*-2-Pentene (major product) — *cis*-2-Pentene — 1-Pentene

(b) The elimination of H_2O from carbons 1 and 2 gives 3-methylcyclopentene; the elimination of H_2O from carbons 1 and 5 gives 4-methylcyclopentene. Because both products are disubstituted alkenes (two carbons bonded to each C—C double bond), they will be formed in approximately equal amounts. Note also that C_3 becomes a stereocenter in 3-methylcyclopentene.



3-Methylcyclopentanol 3-Methylcyclopentene 4-Methylcyclopentene

(c) This reaction initially forms a 2° carbocation intermediate, which rearranges via a 1,2-hydride shift (Section 5.4) to form the more stable 3° carbocation. This new carbocation has three β hydrogens and a C—C double bond can form in three places. 2,3-Dimethyl-2-pentene is the product with the more substituted double bond and is therefore the most stable and major product.



3,4-Dimethyl-2-pentanol

Initial intermediate: a 2° carbocation

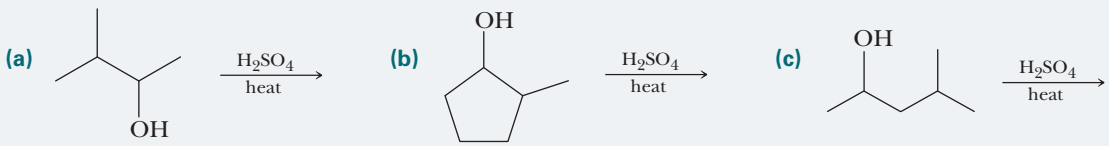
Rearranged intermediate: a 3° carbocation

2-Ethyl-3-methyl-1-butene (*E*)-3,4-Dimethyl-2-pentene (*Z*)-3,4-Dimethyl-2-pentene 2,3-Dimethyl-2-pentene (major product)

See problems 8.41–8.45

PROBLEM 8.5

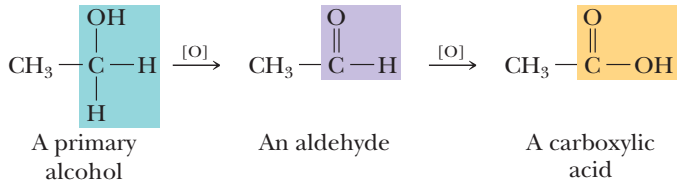
For each of the following alcohols, draw structural formulas for the alkenes that form upon acid-catalyzed dehydration, and predict which alkene is the major product:



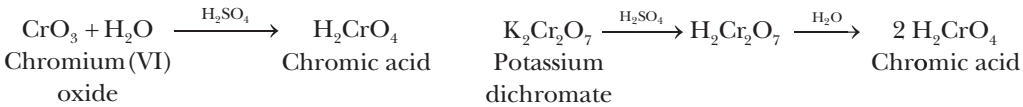
F. Oxidation of Primary and Secondary Alcohols

The oxidation of a primary alcohol gives an aldehyde or a carboxylic acid, depending on the experimental conditions. Secondary alcohols are oxidized to ketones. Tertiary alcohols are not oxidized. Following is a series of transformations in which a primary alcohol is oxidized first to an aldehyde and then to a carboxylic acid. The fact that each

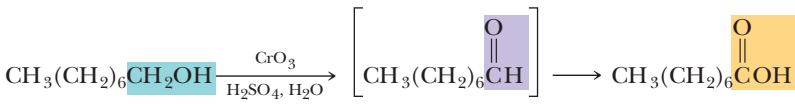
transformation involves oxidation is indicated by the symbol O in brackets over the reaction arrow:

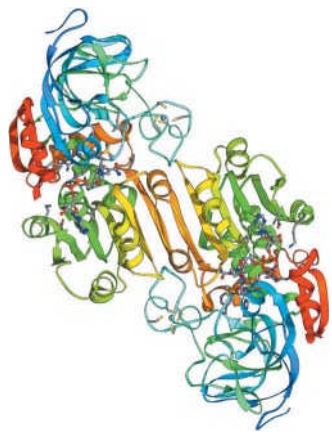


The reagent most commonly used in the laboratory for the oxidation of a primary alcohol to a carboxylic acid and a secondary alcohol to a ketone is chromic acid, H_2CrO_4. Chromic acid is prepared by dissolving either chromium (VI) oxide or potassium dichromate in aqueous sulfuric acid:



The oxidation of 1-octanol by chromic acid in aqueous sulfuric acid gives octanoic acid in high yield. These experimental conditions are more than sufficient to oxidize the intermediate aldehyde to a carboxylic acid:

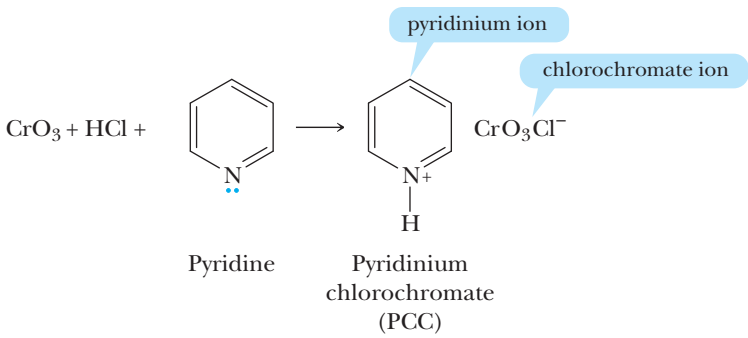




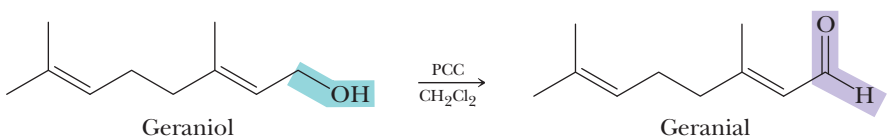
Laguna Design/Science Source Images

In humans, alcohol dehydrogenase is an enzyme that catalyzes the oxidation of ethanol, CH_3CH_2OH, to acetaldehyde, CH_3CHO.

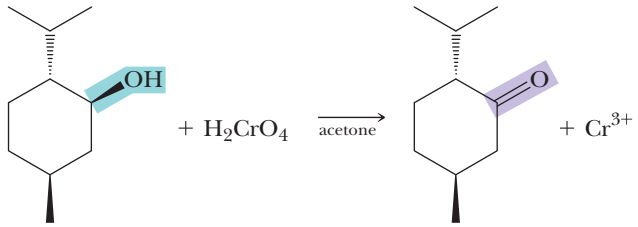
The form of Cr(VI) commonly used for the oxidation of a primary alcohol to an aldehyde is prepared by dissolving CrO_3 in aqueous HCl and adding pyridine to precipitate **pyridinium chlorochromate (PCC)** as a solid. PCC oxidations are carried out in aprotic solvents, most commonly dichloromethane, CH_2Cl_2:



PCC is selective for the oxidation of primary alcohols to aldehydes. It is less reactive than the previously discussed oxidation with chromic acid in aqueous sulfuric acid, and the reaction is run stoichiometrically so that no PCC remains once all the alcohol molecules have been converted to aldehyde. PCC also has little effect on carbon–carbon double bonds or other easily oxidized functional groups. In the following example, geraniol is oxidized to geranial without affecting either carbon–carbon double bond:



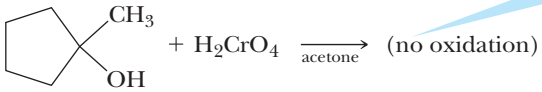
Secondary alcohols are oxidized to ketones by both chromic acid and PCC:



2-Isopropyl-5-methylcyclohexanol (Menthol)

2-Isopropyl-5-methylcyclohexanone (Menthone)

Tertiary alcohols are resistant to oxidation, because the carbon bearing the —OH is bonded to three carbon atoms and therefore cannot form a carbon–oxygen double bond:



although there is no oxidation of a tertiary alcohol, in the presence of an acid catalyst, simple acid-catalyzed dehydration can occur, to give an alkene

1-Methylcyclopentanol

Note that the essential feature of the oxidation of an alcohol is the presence of at least one hydrogen on the carbon bearing the OH group. Tertiary alcohols lack such a hydrogen; therefore, they are not oxidized.

EXAMPLE 8.6

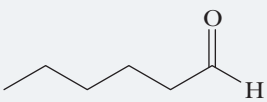
Draw the product of the treatment of each of the following alcohols with PCC:
(a) 1-Hexanol **(b)** 2-Hexanol **(c)** Cyclohexanol

STRATEGY

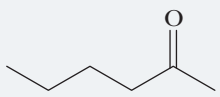
In oxidation reactions of alcohols, identify the type of alcohol as 1°, 2°, or 3°. Tertiary alcohols remain unreactive. Secondary alcohols are oxidized to ketones. Primary alcohols are oxidized to aldehydes when PCC is used as the oxidizing agent, and to carboxylic acids when chromic acid is used as the oxidizing agent.

SOLUTION

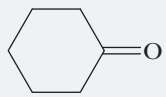
1-Hexanol, a primary alcohol, is oxidized to hexanal. 2-Hexanol, a secondary alcohol, is oxidized to 2-hexanone. Cyclohexanol, a secondary alcohol, is oxidized to cyclohexanone.

(a) 

Hexanal

(b) 

2-Hexanone

(c) 

Cyclohexanone

See problems 8.34, 8.35, 8.38, 8.41–8.46

PROBLEM 8.6

Draw the product of the treatment of each alcohol in Example 8.6 with chromic acid.

8.3 What Are Ethers?

A. Structure

The functional group of an **ether** is an atom of oxygen bonded to two carbon atoms that are part of a hydrocarbon chain or ring. Figure 8.4 shows a Lewis structure and a ball-and-stick model of dimethyl ether, CH_3OCH_3, the simplest ether. In dimethyl ether, two sp^3 hybrid orbitals of oxygen form sigma bonds to carbon atoms. The other two sp^3 hybrid orbitals of oxygen each contain an unshared pair of electrons. The C—O—C bond angle in dimethyl ether is 110.3°, close to the predicted tetrahedral angle of 109.5°.

Ether A compound containing an oxygen atom bonded to two carbon atoms.

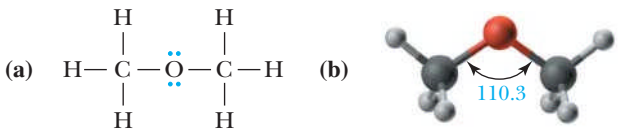


FIGURE 8.4 Dimethyl ether, CH_3OCH_3. (a) Lewis structure and (b) ball-and-stick model.

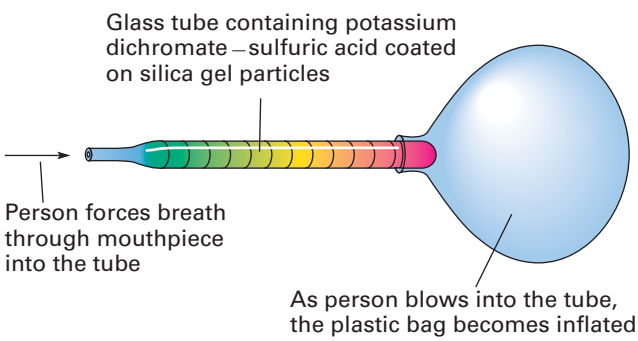
Chemical Connections 8B

BLOOD ALCOHOL SCREENING

Potassium dichromate oxidation of ethanol to acetic acid is the basis for the original breath alcohol screening test used by law enforcement agencies to determine a person's blood alcohol content. The test is based on the difference in color between the dichromate ion (reddish orange) in the reagent and the chromium(III) ion (green) in the product. Thus, color change can be used as a measure of the quantity of ethanol present in a breath sample:

$$\underset{\text{Ethanol}}{CH_3CH_2OH} + \underset{\substack{\text{Dichromate ion}\\ \text{(reddish orange)}}}{Cr_2O_7^{2-}} \xrightarrow[H_2O]{H_2SO_4} \underset{\text{Acetic acid}}{CH_3\overset{\overset{O}{\|}}{C}OH} + \underset{\substack{\text{Chromium(III)}\\ \text{ion (green)}}}{Cr^{3+}}$$

In its simplest form, a breath alcohol screening test consists of a sealed glass tube containing a potassium dichromate–sulfuric acid reagent impregnated on silica gel. To administer the test, the ends of the tube are broken off, a mouthpiece is fitted to one end, and the other end is inserted into the neck of a plastic bag. The person being tested then blows into the mouthpiece until the plastic bag is inflated.

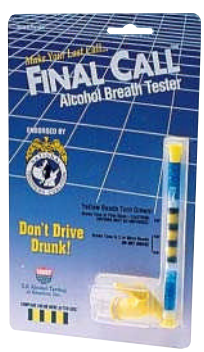


As breath containing ethanol vapor passes through the tube, reddish-orange dichromate ion is reduced to green chromium(III) ion. The concentration of ethanol in the breath is then estimated by measuring how far the green color extends along the length of the tube. When it extends beyond the halfway point, the person is judged as having a sufficiently high blood alcohol content to warrant further, more precise testing.

The Breathalyzer, a more precise testing device, operates on the same principle as the simplified screening test. In a Breathalyzer test, a measured volume of breath is bubbled through a solution of potassium dichromate in aqueous sulfuric acid, and the color change is measured spectrophotometrically.

Both tests measure alcohol in the breath. The legal definition of being under the influence of alcohol is based on *blood* alcohol content, not breath alcohol content. The chemical correlation between these two measurements is that air deep within the lungs is in equilibrium with blood passing through the pulmonary arteries, and an equilibrium is established between blood alcohol and breath alcohol. It has been determined by tests in persons drinking alcohol that 2100 mL of breath contains the same amount of ethanol as 1.00 mL of blood.

Charles D. Winters



A device for testing the breath for the presence of ethanol. When ethanol is oxidized by potassium dichromate, the reddish-orange color of dichromate ion turns to green as it is reduced to chromium(III) ion.

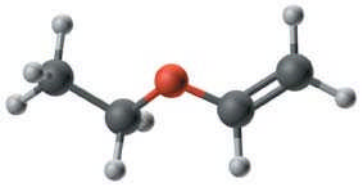
Question
Although methanol* and isopropyl alcohol are much more toxic than ethanol and would rarely be found in one's breath, would these two compounds also give a positive alcohol screening test? If so, what would be the products of these reactions?

*Methanol is indeed much more toxic than ethanol, as many found out during Prohibition when they drank wood alcohol instead of ethanol. Methanol causes damage to the nerve sheaths, and one symptom of methanol poisoning is intense pain in response to light.

In ethyl vinyl ether, the ether oxygen is bonded to one sp^3 hybridized carbon and one sp^2 hybridized carbon:

$CH_3CH_2—O—CH=CH_2$

Ethyl vinyl ether

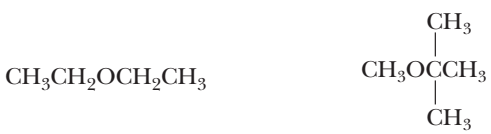


Boston Medical Library in the Francis A. Countway Library of Medicine

This painting by Robert Hinckley shows the first use of diethyl ether as an anesthetic in 1846. Dr. Robert John Collins was removing a tumor from the patient's neck, and the dentist W. T. G. Morton—who discovered its anesthetic properties—administered the ether.

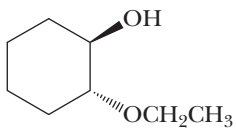
B. Nomenclature

In the IUPAC system, ethers are named by selecting the longest carbon chain as the parent alkane and naming the —OR group bonded to it as an **alkoxy** (*alk*yl + *ox*ygen) **group**. Common names are derived by listing the alkyl groups bonded to oxygen in alphabetical order and adding the word *ether*.



Ethoxyethane
(Diethyl ether)

2-methyl-2-methoxypentanol
(*tert*-Butylmethyl ether)



(1*R*, 2*R*)-2-ethoxycyclohexanol

Chemists almost invariably use common names for low-molecular-weight ethers. For example, although ethoxyethane is the IUPAC name for $CH_3CH_2OCH_2CH_3$, it is rarely called that, but rather is called diethyl ether, ethyl ether, or, even more commonly, simply ether. The abbreviation for *tert*-butyl methyl ether, used at one time as an octane-improving additive to gasolines, is *MTBE*, after the common name of methyl *tert*-butyl ether.

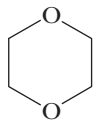
Cyclic ethers are heterocyclic compounds in which the ether oxygen is one of the atoms in a ring. These ethers are generally known by their common names:

Alkoxy group An —OR group, where R is an alkyl group.

Cyclic ethers An ether in which the oxygen is one of the atoms of a ring.

Ethylene oxide

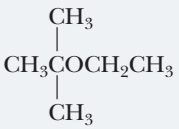
Tetrahydrofuran (THF)

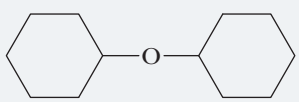


1,4-Dioxane

EXAMPLE 8.7

Write the IUPAC and common names for each ether:

(a) 

(b) 

STRATEGY

As with all nomenclature problems, first determine the root name of the compound. In the IUPAC system, —OR groups are named as alkoxy groups. In the common nomenclature system, the alkyl groups bonded to oxygen are named in alphabetical order, followed by the word "ether."

SOLUTION

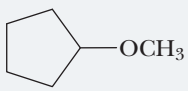
(a) 2-Ethoxy-2-methylpropane. Its common name is *tert*-butyl ethyl ether.
(b) Cyclohexoxycyclohexane. Its common name is dicyclohexyl ether.

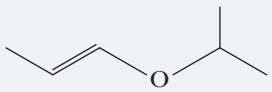
See problem 8.16

PROBLEM 8.7

Write the IUPAC and common names for each ether:

(a) $CH_3CHCH_2OCH_2CH_3$ (with CH_3 branch)

(b) 

(c) 

C. Physical Properties

Ethers are polar compounds in which oxygen bears a partial negative charge and each carbon bonded to it bears a partial positive charge (Figure 8.5). Because of steric hindrance, however, only weak forces of attraction exist between ether molecules in the pure liquid. Consequently, boiling points of ethers are much lower than those of alcohols of comparable molecular weight (Table 8.3). Boiling points of ethers are close to those of hydrocarbons of comparable molecular weight (compare Tables 3.4 and 8.3).

Because the oxygen atom of an ether carries a partial negative charge, ethers form hydrogen bonds with water (Figure 8.6) and are more soluble in water than are hydrocarbons of comparable molecular weight and shape (compare data in Tables 3.4 and 8.3).

The effect of hydrogen bonding is illustrated dramatically by comparing the boiling points of ethanol (78 °C) and its constitutional isomer dimethyl ether (–24 °C). The difference in boiling points between these two compounds is due to the polar O—H group in the alcohol, which is capable of forming intermolecular

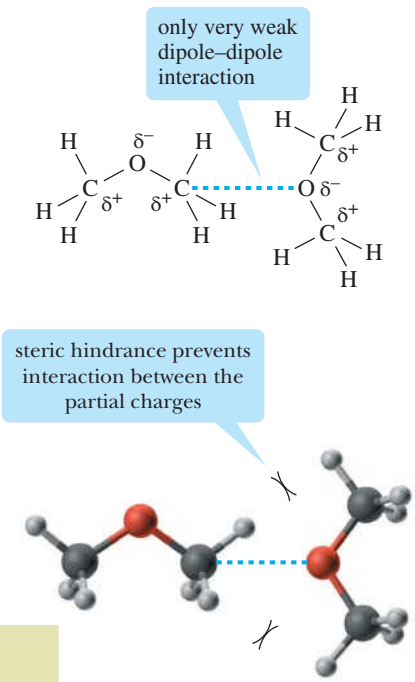


FIGURE 8.5 Ethers are polar molecules, but because of steric hindrance, only weak attractive interactions exist between their molecules in the pure liquid.

TABLE 8.3 Boiling Points and Solubilities in Water of Alcohols and Ethers Grouped by Similar Molecular Weight

Structural Formula	Name	Molecular Weight	Boiling Point (°C)	Solubility in Water
CH_3CH_2OH	ethanol	46	78	infinite
CH_3OCH_3	dimethyl ether	46	–24	7.8 g/100 g
$CH_3CH_2CH_2CH_2OH$	1-butanol	74	117	7.4 g/100 g
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	8 g/100 g
$CH_3CH_2CH_2CH_2CH_2OH$	1-pentanol	88	138	2.3 g/100 g
$HOCH_2CH_2CH_2CH_2OH$	1,4-butanediol	90	230	infinite
$CH_3CH_2CH_2CH_2OCH_3$	butyl methyl ether	88	71	slight
$CH_3CH_2CH_2CH_2OCH_3$	ethylene glycol dimethyl ether	90	84	infinite

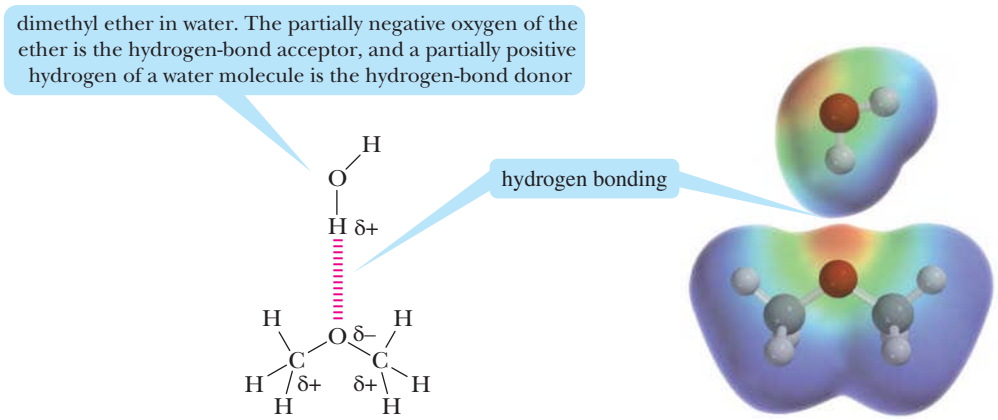


FIGURE 8.6 Ethers are hydrogen-bond acceptors only. They are not hydrogen-bond donors.

hydrogen bonds. This hydrogen bonding increases the attractive force between molecules of ethanol; thus, ethanol has a higher boiling point than dimethyl ether:

CH_3CH_2OH	CH_3OCH_3
Ethanol	Dimethyl ether
bp 78 °C	bp −24 °C

EXAMPLE 8.8

Arrange these compounds in order of increasing solubility in water:

$CH_3OCH_2CH_2OCH_3$	$CH_3CH_2OCH_2CH_3$	$CH_3CH_2CH_2CH_2CH_2CH_3$
Ethylene glycol dimethyl ether	Diethyl ether	Hexane

STRATEGY

Look for features that make organic compounds more soluble in water. These are, from most significant to least significant, (1) the ability to form hydrogen bonds with water, (2) polarity, and (3) low molecular weight.

SOLUTION

Water is a polar solvent. Hexane, a nonpolar hydrocarbon, has the lowest solubility in water. Both diethyl ether and ethylene glycol dimethyl ether are polar compounds, due to the presence of their polar C—O—C groups, and each interacts with water as a hydrogen-bond acceptor. Because ethylene glycol dimethyl ether has more sites within its molecules for hydrogen bonding, it is more soluble in water than diethyl ether:

$CH_3CH_2CH_2CH_2CH_2CH_3$	$CH_3CH_2OCH_2CH_3$	$CH_3OCH_2CH_2OCH_3$
Insoluble	8g/100 g water	Soluble in all proportions

See problems 8.23–8.25

PROBLEM 8.8

Arrange these compounds in order of increasing boiling point:

$CH_3OCH_2CH_2OCH_3$ $HOCH_2CH_2OH$ $CH_3OCH_2CH_2OH$

D. Reactions of Ethers

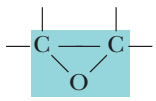
Ethers, R—O—R, resemble hydrocarbons in their resistance to chemical reaction. They do not react with oxidizing agents, such as potassium dichromate or potassium permanganate. They are not affected by most acids or bases at moderate temperatures. Because of their good solvent properties and general inertness to chemical reaction, ethers are excellent solvents in which to carry out many organic reactions.

8.4 What Are Epoxides?

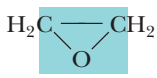
A. Structure and Nomenclature

Epoxide A cyclic ether in which oxygen is one atom of a three-membered ring.

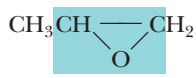
An **epoxide** is a cyclic ether in which oxygen is one atom of a three-membered ring:



Functional group of an epoxide



Ethylene oxide



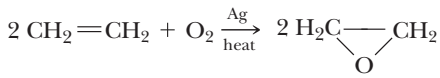
Propylene oxide

Although epoxides are technically classed as ethers, we discuss them separately because of their exceptional chemical reactivity compared with other ethers.

Common names for epoxides are derived by giving the common name of the alkene from which the epoxide might have been derived, followed by the word *oxide*; an example is ethylene oxide.

B. Synthesis from Alkenes

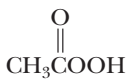
Ethylene oxide, one of the few epoxides manufactured on an industrial scale, is prepared by passing a mixture of ethylene and air (or oxygen) over a silver catalyst:



Ethylene — Ethylene oxide

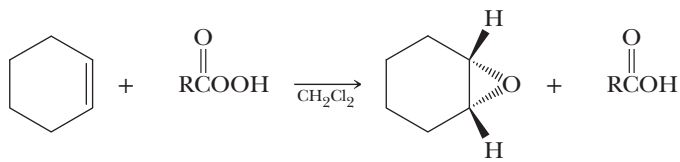
In the United States, the annual production of ethylene oxide by this method is approximately 10^9 kg.

The most common laboratory method for the synthesis of epoxides from alkenes is oxidation with a peroxycarboxylic acid (a peracid), RCO_3H. One peracid used for this purpose is peroxyacetic acid:



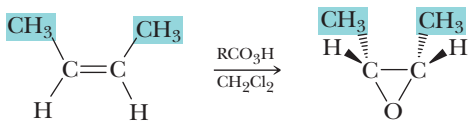
Peroxyacetic acid
(Peracetic acid)

Following is a balanced equation for the epoxidation of cyclohexene by a peroxycarboxylic acid. In the process, the peroxycarboxylic acid is reduced to a carboxylic acid:



Cyclohexene — A peroxycarboxylic acid — 1,2-Epoxycyclohexane (Cyclohexene oxide) — A carboxylic acid

The epoxidation of an alkene is stereoselective. The epoxidation of *cis*-2-butene, for example, yields only *cis*-2-butene oxide:

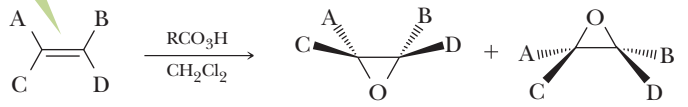


cis-2-Butene — *cis*-2-Butene oxide

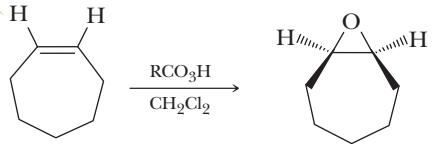
HOW TO 8.5 Predict the Product of an Epoxidation Reaction

The key feature of an epoxidation reaction of an alkene and a peroxycarboxylic acid is the formation of an epoxide with retention of stereochemistry about the reacting C—C double bond. This means that the relative stereochemistry of all groups about the double bond must be the same in the product epoxide as shown in the acyclic and cyclic examples.

groups that are *trans* in the alkene, such as groups C and B, will be *trans* in the epoxide



because the vinylic hydrogens are *cis* in the reactant, they must remain *cis* in the product



EXAMPLE 8.9

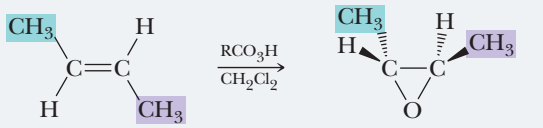
Draw a structural formula of the epoxide formed by treating *trans*-2-butene with a peroxycarboxylic acid.

STRATEGY

To predict the product of a peroxycarboxylic acid and an alkene, convert its C—C double bond to a C—C single bond in which both carbons are bonded to the same oxygen in a three-membered ring.

SOLUTION

The oxygen of the epoxide ring is added by forming both carbon–oxygen bonds from the same side of the carbon–carbon double bond:



trans-2-Butene *trans*-2-Butene oxide

See problems 8.43–8.45, 8.47

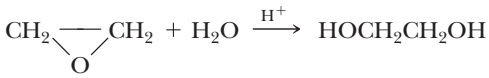
PROBLEM 8.9

Draw the structural formula of the epoxide formed by treating 1,2-dimethylcyclopentene with a peroxycarboxylic acid.

C. Ring-Opening Reactions

Ethers are not normally susceptible to reaction with aqueous acid (Section 8.3D). Epoxides, however, are especially reactive because of the angle strain in the three-membered ring. The normal bond angle about an sp^3 hybridized carbon or oxygen atom is 109.5°. Because of the strain associated with the compression of bond angles in the three-membered epoxide ring from the normal 109.5° to 60°, epoxides undergo ring-opening reactions with a variety of nucleophilic reagents.

In the presence of an acid catalyst—most commonly, perchloric acid—epoxides are hydrolyzed to glycols. As an example, the acid-catalyzed hydrolysis of ethylene oxide gives 1,2-ethanediol:

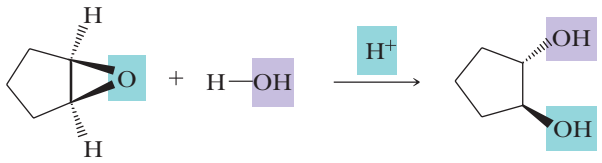


Ethylene oxide 1,2-Ethanediol (Ethylene glycol)

Annual production of ethylene glycol in the United States is approximately 10^{10} kg. Two of its largest uses are in automotive antifreeze and as one of the two starting materials for the

production of polyethylene terephthalate (PET), which is fabricated into such consumer products as Dacron® polyester, Mylar®, and packaging films (Section 17.4B).

The acid-catalyzed ring opening of epoxides shows a stereoselectivity typical of S_N2 reactions: The nucleophile attacks anti to the leaving hydroxyl group, and the —OH groups in the glycol thus formed are anti. As a result, the acid-catalyzed hydrolysis of an epoxycycloalkane yields a *trans*-1,2-cycloalkanediol:



Normally, epoxides will not react with H_2O because water is a poor nucleophile. The mechanism below shows how the acid catalyst makes it possible for the epoxide to react with water.

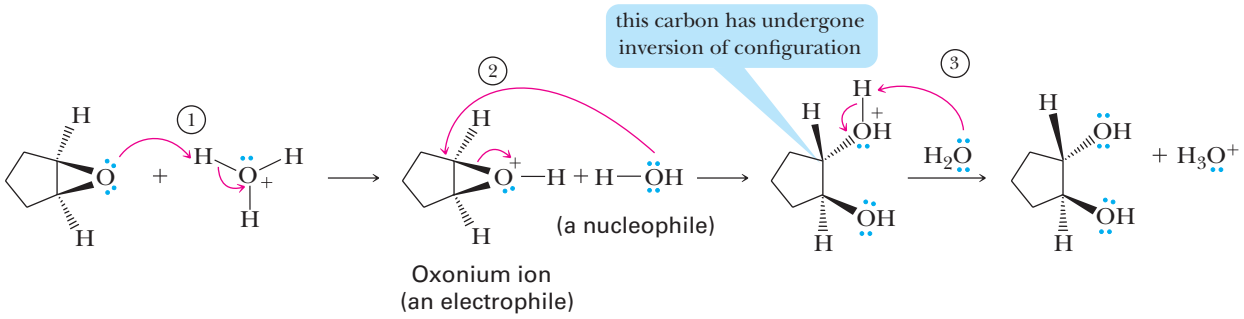
Mechanism

Acid-Catalyzed Epoxide Ring Opening

STEP 1: *Add a proton.*
The reaction is made possible because the acid catalyst protonates the epoxide oxygen, generating a highly reactive oxonium ion.

STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*
The positive charge on the oxygen of the three-membered ring makes one of the epoxide carbons susceptible to nucleophilic attack by water. This opens the epoxide with inversion of configuration at the carbon that was attacked.

STEP 3: *Take a proton away.*
Transfer of a proton from the resulting intermediate gives the *trans* glycol and regenerates the acid.



EXAMPLE 8.10

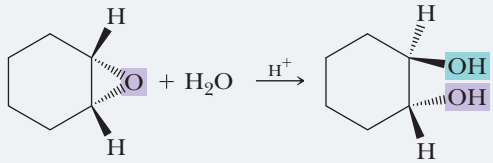
Draw the structural formula of the product formed by treating cyclohexene oxide with aqueous acid. Be certain to show the stereochemistry of the product.

STRATEGY

The acid-catalyzed ring opening of an epoxide always results in a *trans*-1,2,-diol, with the two carbons formerly part of the epoxide bonded to each of the two hydroxyl groups.

SOLUTION

The acid-catalyzed hydrolysis of the three-membered epoxide ring gives a *trans* glycol:

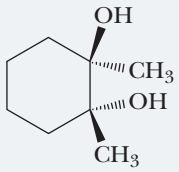


trans-1,2-Cyclohexanediol

See problems 8.26, 8.43–8.45

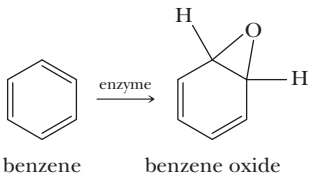
PROBLEM 8.10

Show how to convert 1,2-dimethylcyclohexene to *trans*-1,2-dimethylcyclohexane-1,2-diol.



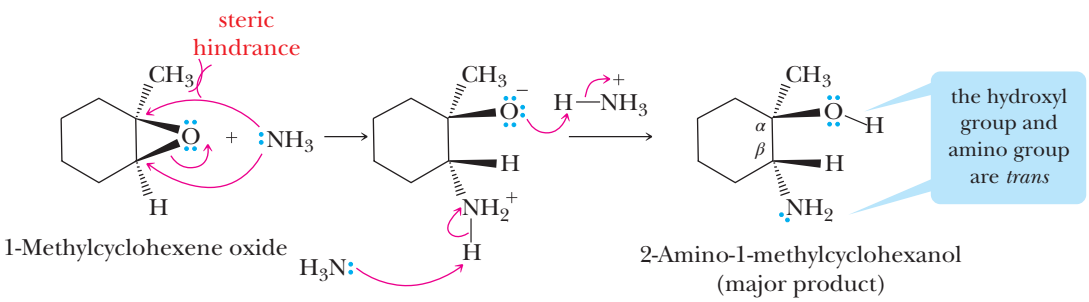
trans-1,2-Dimethylcyclohexane-1,2-diol

Just as ethers are not normally susceptible to reaction with electrophiles, neither are they normally susceptible to reaction with nucleophiles. Because of the strain associated with the three-membered ring, however, epoxides undergo ring-opening reactions with good nucleophiles such as ammonia and amines (Chapter 10), alkoxide ions, and thiols and their anions (Section 8.6). Good nucleophiles attack the ring by an S_N2 mechanism and show a stereoselectivity for attack of the nucleophile at the less hindered carbon of the three-membered ring. The result is an alcohol with the former nucleophile bonded to a carbon β to the newly formed hydroxyl group. An illustration is the reaction of 1-methylcyclohexene oxide with ammonia to give the stereoisomer of 2-amino-1-methylcyclohexanol in which the hydroxyl group and the amino group are *trans*:



benzene benzene oxide

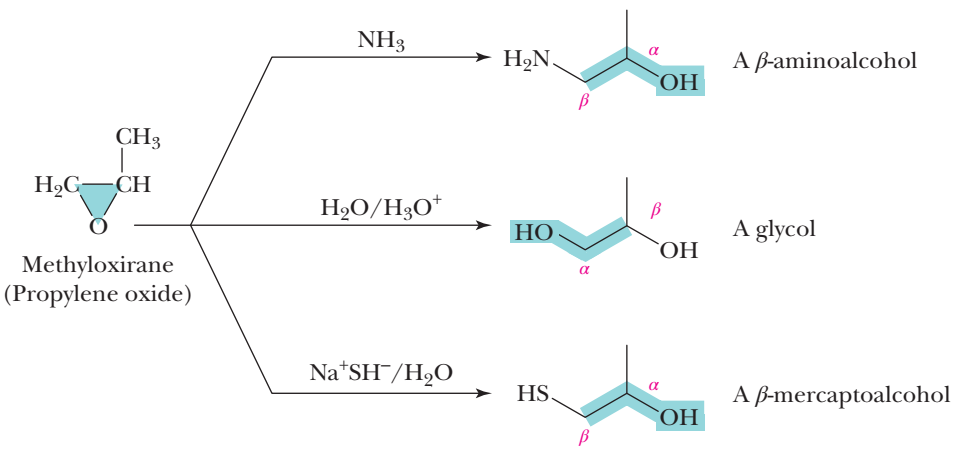
When humans are exposed to benzene, the body uses an enzyme to oxidize it to benzene oxide. This epoxide is highly reactive, leading to nucleophilic attack by DNA and subsequent adverse health issues.



1-Methylcyclohexene oxide

2-Amino-1-methylcyclohexanol (major product)

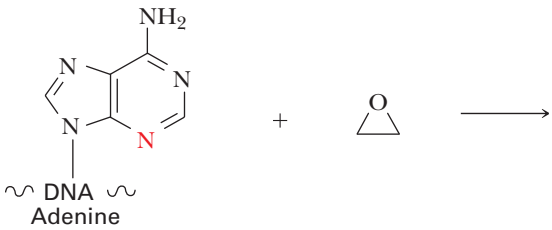
The value of epoxides lies in the number of nucleophiles that bring about ring opening and the combinations of functional groups that can be prepared from them. The following chart summarizes the three most important of these nucleophilic ring-opening reactions (the characteristic structural feature of each ring-opening product is shown in color):



Chemical Connections 8C

ETHYLENE OXIDE: A CHEMICAL STERILANT

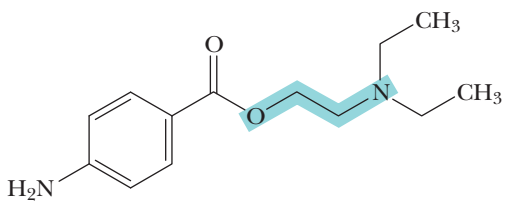
Because ethylene oxide is such a highly strained molecule, it reacts with the types of nucleophilic groups present in biological materials. At sufficiently high concentrations, ethylene oxide reacts with enough molecules in cells to cause the death of microorganisms. This toxic property is the basis for using ethylene oxide as a chemical sterilant. In hospitals, surgical instruments and other items that cannot be made disposable are now sterilized by exposure to ethylene oxide.



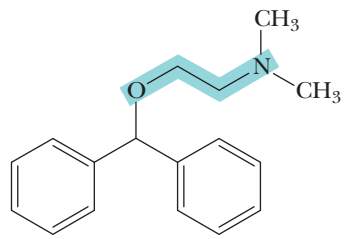
Question

One of the ways that ethylene oxide has been found to kill microorganisms is by reacting with the adenine components of their DNA at the atom indicated in red. Propose a mechanism and an initial product for this reaction. *Hint:* First draw in any lone pairs of electrons in adenine.

Ethylene oxide and substituted ethylene oxides are valuable building blocks for the synthesis of larger organic molecules. Following are structural formulas for two common drugs, each synthesized in part from ethylene oxide:



Procaine
(Novocaine)



Diphenhydramine
(Benadryl)

Novocaine was the first injectable local anesthetic. Benadryl was the first synthetic antihistamine. The portion of the carbon skeleton of each that is derived from the reaction of ethylene oxide with a nitrogen–nucleophile is shown in color.

In later chapters, after we have developed the chemistry of more functional groups, we will show how to synthesize Novocaine and Benadryl from readily available starting materials. For the moment, however, it is sufficient to recognize that the unit —O—C—C—Nu can be derived by nucleophilic opening of ethylene oxide or a substituted ethylene oxide.

Stephen J. Krasemann/
Photo Researchers, Inc.

The scent of skunks is a mixture of two thiols, 3-methyl-1-butanethiol and 2-butene-1-thiol.

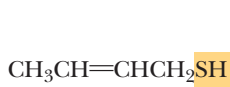
Thiol A compound containing an —SH (sulfhydryl) group.

8.5 What Are Thiols?

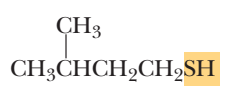
A. Structure

The functional group of a **thiol** is an —SH (sulfhydryl) group. Figure 8.7 shows a Lewis structure and a ball-and-stick model of methanethiol, CH_3SH, the simplest thiol.

The most outstanding property of low-molecular-weight thiols is their stench. They are responsible for the unpleasant odors such as those from skunks, rotten eggs, and sewage. The scent of skunks is due primarily to two thiols:



2-Butene-1-thiol



3-Methyl-1-butanethiol

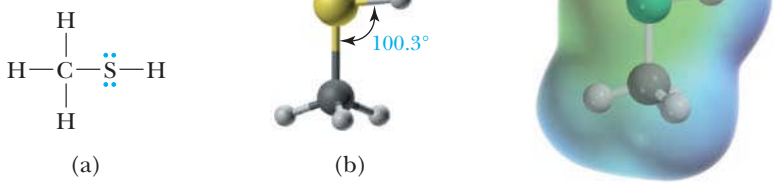
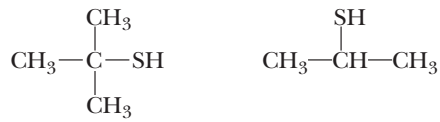


FIGURE 8.7 Methanethiol, CH_3SH. (a) Lewis structure and (b) ball-and-stick model. The C—S—H bond angle is 100.3°, somewhat smaller than the tetrahedral angle of 109.5°.

Methanethiol. The electronegativities of carbon and sulfur are virtually identical (2.5 each), while sulfur is slightly more electronegative than hydrogen (2.5 versus 2.1). The electron density model shows some slight partial positive charge on hydrogen of the S—H group and some slight partial negative charge on sulfur.

A blend of low-molecular-weight thiols is added to natural gas as an odorant. The most common of these odorants is 2-methyl-2-propanethiol (*tert*-butyl mercaptan) because it is the most resistant to oxidation and has the greatest soil penetration. 2-Propanethiol is also used for this purpose, usually as a blend with *tert*-butyl mercaptan.

Natural gas odorants:



2-Methyl-2-propanethiol (*tert*-Butyl mercaptan)

2-Propanethiol (Isopropyl mercaptan)

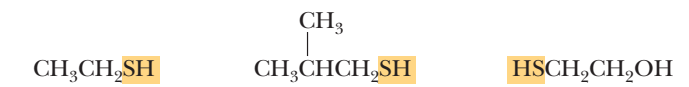
B. Nomenclature

Mercaptan A common name for any molecule containing an —SH group.

The sulfur analog of an alcohol is called a thiol (thi- from the Greek: *theion*, sulfur) or, in the older literature, a **mercaptan**, which literally means "mercury capturing." Thiols react with Hg^{2+} in aqueous solution to give sulfide salts as insoluble precipitates. Thiophenol, C_6H_5SH, for example, gives $(C_6H_5S)_2Hg$.

In the IUPAC system, thiols are named by selecting as the parent alkane the longest chain of carbon atoms that contains the —SH group. To show that the compound is a thiol, we add *-thiol* to the name of the parent alkane and number the parent chain in the direction that gives the —SH group the lower number.

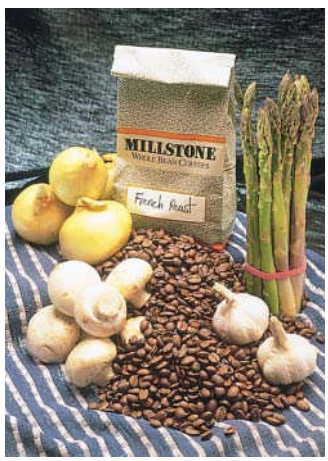
Common names for simple thiols are derived by naming the alkyl group bonded to —SH and adding the word *mercaptan*. In compounds containing other functional groups, the presence of an —SH group is indicated by the prefix **mercapto-**. According to the IUPAC system, —OH takes precedence over —SH in both numbering and naming:



Ethanethiol (Ethyl mercaptan)

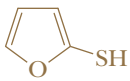
2-Methyl-1-propanethiol (Isobutyl mercaptan)

2-Mercaptoethanol



Charles D. Winters

Mushrooms, onions, garlic, and coffee all contain sulfur compounds. One of these present in coffee is



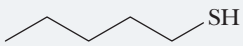
Sulfur analogs of ethers (thioethers) are named by using the word *sulfide* to show the presence of the —S— group. Following are common names of two sulfides:

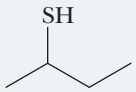
Dimethyl sulfide

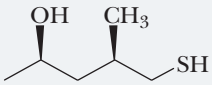
Ethyl isopropyl sulfide

EXAMPLE 8.11

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

STRATEGY

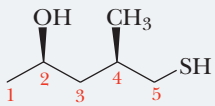
Identify the root name of the compound. If the compound only contains an —SH group, name it as an alkanethiol. If the compound contains both an —OH group and an —SH group, name the compound as an alcohol with a mercapto substituent. Remember that priority for numbering is given to the —OH group.

SOLUTION

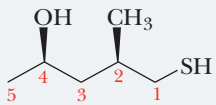
(a) The parent alkane is pentane. We show the presence of the —SH group by adding *thiol* to the name of the parent alkane. The IUPAC name of this thiol is 1-pentanethiol. Its common name is pentyl mercaptan.

(b) The parent alkane is butane. The IUPAC name of this thiol is 2-butanethiol. Its common name is *sec*-butyl mercaptan. It is a chiral molecule due to the stereocenter at C-2. However, the stereochemical configuration was not indicated here.

(c) The parent alkane is pentane. Because —OH receives priority over —SH, the compound is named as an alcohol, with the —OH group receiving priority for numbering as well.



not

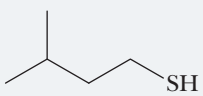


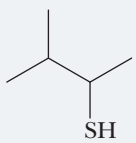
(2*R*,4*R*)-5-Mercapto-4-methylpentan-2-ol

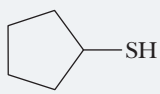
See problems 8.14, 8.15

PROBLEM 8.11

Write the IUPAC name for each thiol:

(a) 

(b) 

(c) 

C. Physical Properties

Because of the small difference in electronegativity between sulfur and hydrogen $(2.5 - 2.1 = 0.4)$, we classify the S—H bond as nonpolar covalent. Because of this lack of polarity, thiols show little association by hydrogen bonding. Consequently, they have lower boiling points and are less soluble in water and other polar solvents than are alcohols of similar molecular weight. Table 8.4 gives the boiling points of three low-molecular-weight thiols. For comparison, the table also gives the boiling points of alcohols with the same number of carbon atoms.

Earlier, we illustrated the importance of hydrogen bonding in alcohols by comparing the boiling points of ethanol (78 °C) and its constitutional isomer dimethyl ether (24 °C).

TABLE 8.4 Boiling Points of Three Thiols and Three Alcohols with the Same Number of Carbon Atoms

Thiol	Boiling Point (°C)	Alcohol	Boiling Point (°C)
methanethiol	6	methanol	65
ethanethiol	35	ethanol	78
1-butanethiol	98	1-butanol	117

By comparison, the boiling point of ethanethiol is 35 °C, and that of its constitutional isomer dimethyl sulfide is 37 °C:

CH_3CH_2SH	CH_3SCH_3
Ethanethiol	Dimethyl sulfide
bp 35 °C	bp 37 °C

The fact that the boiling points of these constitutional isomers are almost identical indicates that little or no association by hydrogen bonding occurs between thiol molecules.

8.6 What Are the Characteristic Reactions of Thiols?

In this section, we discuss the acidity of thiols and their reaction with strong bases, such as sodium hydroxide, and with molecular oxygen.

A. Acidity

Hydrogen sulfide is a stronger acid than water:

$$H_2O + H_2O \rightleftharpoons HO^- + H_3O^+ \qquad pK_a = 15.7$$
$$H_2S + H_2O \rightleftharpoons HS^- + H_3O^+ \qquad pK_a = 7.0$$

Similarly, thiols are stronger acids than alcohols. Compare, for example, the pK_a's of ethanol and ethanethiol in dilute aqueous solution:

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \qquad pK_a = 15.9$$
$$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+ \qquad pK_a = 8.5$$

thiols are more acidic than alcohols because sulfides are more stable conjugate bases than are alkoxides. There is more area to delocalize the valence electrons about the negative sulfur atom because sulfur is larger than oxygen.

Thiols are sufficiently strong acids that, when dissolved in aqueous sodium hydroxide, they are converted completely to alkylsulfide salts:

$$CH_3CH_2SH + Na^+OH^- \longrightarrow CH_3CH_2S^-\,Na^+ + H_2O$$

pK_a 8.5			pK_a15.7
Stronger acid	Stronger base	Weaker base	Weaker acid

To name salts of thiols, give the name of the cation first, followed by the name of the alkyl group to which the suffix *-sulfide* is added. For example, the sodium salt derived from ethanethiol is named sodium ethylsulfide.

B. Oxidation to Disulfides

Many of the chemical properties of thiols stem from the fact that the sulfur atom of a thiol is oxidized easily to several higher oxidation states. The most common reaction of thiols in biological systems is their oxidation to disulfides, the functional group of which is a **disulfide** (—S—S—) bond. Thiols are readily oxidized to disulfides by molecular oxygen. In fact, they are so susceptible to oxidation that they must be protected from contact with air during storage. Disulfides, in turn, are easily reduced to thiols by several reagents. This easy interconversion between thiols and disulfides is very important in protein chemistry, as we will see in Chapter 18:

$$2\ HOCH_2CH_2SH \underset{\text{reduction}}{\overset{\text{oxidation}}{\rightleftharpoons}} HOCH_2CH_2S{-}SCH_2CH_2OH$$

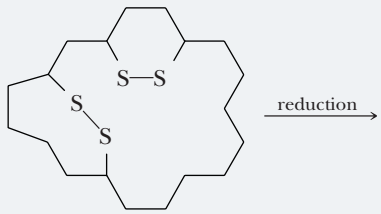
A thiol — A disulfide

We derive common names of simple disulfides by listing the names of the groups bonded to sulfur and adding the word *disulfide*, as, for example, $CH_3S{-}SCH_3$, which is named dimethyldisulfide.

EXAMPLE 8.12

Predict the products of the following reactions. If the reaction is an acid–base reaction, predict its position of equilibrium.

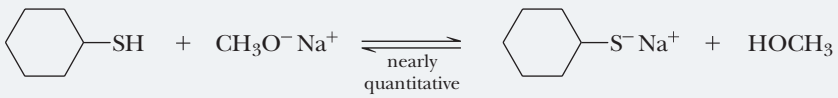
(a) 

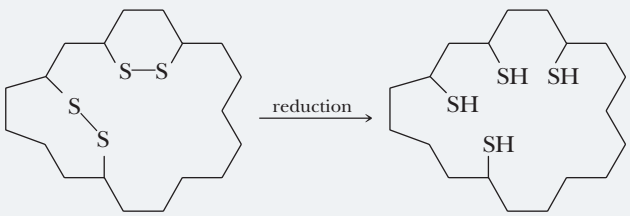
(b) 

STRATEGY

First determine what type of reaction is occurring. An oxidation reaction of a thiol produces a disulfide bond (—S—S—). A reduction of a disulfide bond produces two mercapto groups. Thiols can also act as weak acids (although at a pK_a of 8.5, they are relatively strong for an organic acid).

SOLUTION

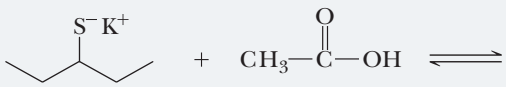
(a) 

(b) 

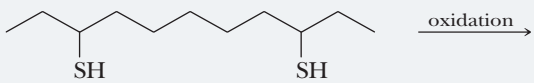
See problems 8.28–8.30, 8.32

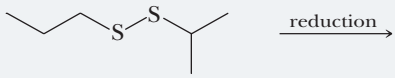
PROBLEM 8.12

Predict the products of the following reactions. If the reaction is an acid–base reaction, predict its position of equilibrium.

(a) 

(b) 

(c) 

(d) 

SUMMARY OF KEY QUESTIONS

8.1 What Are Alcohols?

- The functional group of an **alcohol** is an —OH (**hydroxyl**) **group** bonded to an sp^3 hybridized carbon.
- Alcohols are classified as 1°, 2°, or 3°, depending on whether the —OH group is bonded to a primary, secondary, or tertiary carbon.
- IUPAC names of alcohols are derived by changing the suffix of the parent alkane from *-e* to *-ol*. The chain is numbered to give the carbon bearing —OH the lower number.
- Common names for alcohols are derived by naming the alkyl group bonded to —OH and adding the word *alcohol*.
- Alcohols are polar compounds with oxygen bearing a partial negative charge and both the carbon and hydrogen bonded to it bearing partial positive charges.
- Because of intermolecular association by hydrogen bonding, the boiling points of alcohols are higher than those of hydrocarbons with comparable molecular weight.
- Because of increased dispersion forces, the boiling points of alcohols increase with increasing molecular weight.
- Alcohols interact with water by **hydrogen bonding** and therefore are more soluble in water than are hydrocarbons of comparable molecular weight.

8.2 What Are the Characteristic Reactions of Alcohols?

- Alcohols undergo acid–base reactions, acting both as weak acids and weak bases. The two smallest alcohols, methanol and ethanol, are comparable to water in acidity, while most 2° and 3° alcohols are less acidic than water.
- Alcohols react with **active metals** (e.g., Li, Na, K) to give **alkoxides**.
- Alcohols react with hydrogen halides (HCl, HBr, and HI) to give haloalkanes via substitution reactions. The mechanism of the reaction is either S_N1 or S_N2 depending on the classification (1°, 2°, or 3°) of the alcohol.
- Alcohols react with **thionyl chloride**, $SOCl_2$, to give chloroalkanes.
- Alcohols undergo **dehydration** in concentrated sulfuric or phosphoric acid. These elimination reactions follow Zaitsev's rule, yielding the more substituted alkene as the major product.
- Alcohols can be **oxidized** to ketones, aldehydes, and carboxylic acids. **Chromic acid** and **pyridinium chlorochromate** (PCC) both oxidize 2° alcohols to ketones. PCC oxidizes 1° alcohols to aldehydes, while chromic acid oxidizes 1° alcohols to carboxylic acids. 3° Alcohols are not oxidized.

8.3 What Are Ethers?

- The functional group of an **ether** is an atom of oxygen bonded to two carbon atoms. Ethers are used as solvents and in medicine as inhalation anesthetics.
- In the IUPAC name of an ether, the parent alkane is named, and then the —OR group is named as an alkoxy substituent. Common names are derived by naming the two groups bonded to oxygen followed by the word "ether". Ethers are weakly polar compounds. Their boiling points are close to those of hydrocarbons with comparable molecular weight. Because ethers are hydrogen-bond acceptors, they are more soluble in water than are hydrocarbons with comparable molecular weight.
- Ethers are relatively resistant to chemical transformation and, for this reason, are often employed as solvents in chemical reactions.

8.4 What Are Epoxides?

- An **epoxide** is a three-membered cyclic ether in which oxygen is one of the atoms of the three-membered ring.
- Epoxides can be synthesized from the reaction of an alkene with a **peroxycarboxylic acid** (RCO_3H). The reaction proceeds such that the relative stereochemistry about the C—C double bond is retained in the product epoxide.
- Epoxides undergo ring-opening reactions due to the strain of their three-membered rings. In acid-catalyzed hydrolysis, epoxides made from cyclic alkenes are transformed into *trans*-glycols. Good nucleophiles can also open the epoxide ring via nucleophilic attack at the least substituted carbon of the three-membered ring.

8.5 What Are Thiols?

- A **thiol** is the sulfur analog of an alcohol; it contains an —SH **(sulfhydryl) group** in place of an —OH group. Thiols are important compounds in several biological processes.
- Thiols are named in the same manner as alcohols, but the suffix *-e* is retained, and *-thiol* is added. Common names for thiols are derived by naming the alkyl group bonded to —SH and adding the word "**mercaptan**". In compounds containing functional groups of higher precedence, the presence of —SH is indicated by the prefix **mercapto-**. For thioethers, name the two groups bonded to sulfur, followed by the word **"sulfide."**
- The S—H bond is nonpolar covalent, and the physical properties of thiols are more like those of hydrocarbons with comparable molecular weight.

8.6 What Are the Characteristic Reactions of Thiols?

- Thiols ($pK_a \approx 8.5$) are stronger acids than alcohols and are quantitatively deprotonated by hydroxide.
- Thiols can be oxidized to give a **disulfide** (—S—S—) bond. This process is reversible through reduction.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Dehydration of an alcohol proceeds either by an E1 or an E2 mechanism. (8.2)
2. Epoxides are more reactive than acyclic ethers. (8.3, 8.4)
3. Attack of an electrophile on the carbon of an epoxide ring results in opening of the ring. (8.4)
4. A hydrogen bond is a form of dipole–dipole interaction. (8.1)
5. Alcohols have higher boiling points than thiols with the same molecular weight. (8.1, 8.5)
6. Thiols are more acidic than alcohols. (8.2, 8.5)
7. Alcohols can act as hydrogen-bond donors but not as hydrogen-bond acceptors. (8.1)
8. Alcohols can function as both acids and bases. (8.2)

9. Ethers can act as hydrogen-bond donors but not as hydrogen-bond acceptors. (8.3)

10. Reduction of a thiol produces a disulfide. (8.6)

11. Ethers are more reactive than alcohols. (8.2, 8.3)

12. $(CH_3CH_2)_2CHOH$ is classified as a 3° alcohol. (8.1)

13. PCC will oxidize a secondary alcohol to a ketone. (8.2)

14. PCC will oxidize a primary alcohol to a carboxylic acid. (8.2)

15. Alcohols have higher boiling points than ethers with the same molecular weight. (8.1, 8.3)

16. A dehydration reaction yields an epoxide as the product. (8.2)

17. Alcohols can be converted to alkenes. (8.2)

18. Alcohols can be converted to haloalkanes. (8.2)

19. In naming alcohols, "alkyl alcohol" is the IUPAC form of the name, while "alkanol" is the common form of the name. (8.1)

20. —OH is a poor leaving group. (8.2)

21. A glycol is any alcohol with at least two hydroxyl groups bonded to different carbons. (8.1)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) T (3) F (4) T (5) T (6) T (7) F (8) T (9) F (10) F (11) F (12) F (13) T (14) F (15) T (16) F (17) T (18) T (19) F (20) T (21) T

KEY REACTIONS

1. **Acidity of Alcohols (Section 8.2A)**
In dilute aqueous solution, methanol and ethanol are comparable in acidity to water. Secondary and tertiary alcohols are weaker acids than water.

$$CH_3OH + H_2O \rightleftharpoons CH_3O^- + H_3O^+ \quad pK_a = 15.5$$

2. **Reaction of Alcohols with Active Metals (Section 8.2C)**
Alcohols react with Li, Na, K, and other active metals to form metal alkoxides, which are somewhat stronger bases than NaOH and KOH:

$$2\ CH_3CH_2OH + 2\ Na \longrightarrow 2\ CH_3CH_2O^-Na^+ + H_2$$

3. **Reaction of Alcohols with HCl, HBr, and HI (Section 8.2D)**
Primary alcohols react with HBr and HI by an S_N2 mechanism:

$$CH_3CH_2CH_2CH_2OH + HBr \longrightarrow CH_3CH_2CH_2CH_2Br + H_2O$$

Tertiary alcohols react with HCl, HBr, and HI by an S_N1 mechanism, with the formation of a carbocation intermediate:

$$(CH_3)_3COH + HCl \xrightarrow{25\ ^\circ C} (CH_3)_3CCl + H_2O$$

Secondary alcohols may react with HCl, HBr, and HI by an S_N2 or an S_N1 mechanism, depending on the alcohol and experimental conditions.

4. **Reaction of Alcohols with $SOCl_2$ (Section 8.2D)**
This is often the method of choice for converting an alcohol to an alkyl chloride:

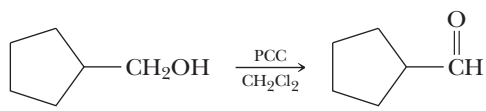
$$CH_3(CH_2)_5OH + SOCl_2 \longrightarrow CH_3(CH_2)_5Cl + SO_2 + HCl$$

5. **Acid-Catalyzed Dehydration of Alcohols (Section 8.2E)**
When isomeric alkenes are possible, the major product is generally the more substituted alkene (Zaitsev's rule):

$$CH_3CH_2CH(OH)CH_3 \xrightarrow[\text{heat}]{H_3PO_4} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2 + H_2O$$

Major product

6. **Oxidation of a Primary Alcohol to an Aldehyde (Section 8.2F)**
This oxidation is most conveniently carried out by using pyridinium chlorochromate (PCC):



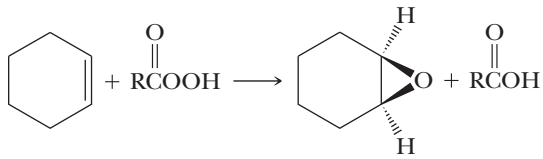
7. **Oxidation of a Primary Alcohol to a Carboxylic Acid (Section 8.2F)**
A primary alcohol is oxidized to a carboxylic acid by chromic acid:

$$CH_3(CH_2)_4CH_2OH + H_2CrO_4 \xrightarrow[\text{acetone}]{H_2O} CH_3(CH_2)_4COH + Cr^{3+}$$

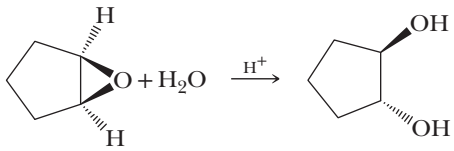
8. **Oxidation of a Secondary Alcohol to a Ketone (Section 8.2F)**
A secondary alcohol is oxidized to a ketone by chromic acid and by PCC:

$$CH_3(CH_2)_4CH(OH)CH_3 + H_2CrO_4 \longrightarrow CH_3(CH_2)_4C(=O)CH_3 + Cr^{3+}$$

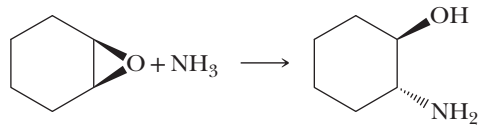
9. **Oxidation of an Alkene to an Epoxide (Section 8.4B)**
The most common method for the synthesis of an epoxide from an alkene is oxidation with a peroxycarboxylic acid, such as peroxyacetic acid:



10. Acid-Catalyzed Hydrolysis of Epoxides (Section 8.4C)
Acid-catalyzed hydrolysis of an epoxide derived from a cycloalkene gives a *trans* glycol (hydrolysis of cycloalkene oxide is stereoselective, giving the *trans* glycol):



11. Nucleophilic Ring Opening of Epoxides (Section 8.4C)
Good nucleophiles, such as ammonia and amines, open the highly strained epoxide ring by an S_N2 mechanism and show a regioselectivity for attack of the nucleophile at the less hindered carbon of the three-membered ring. The reaction favors the stereoselective formation of the *trans* product:



Cyclohexene oxide *trans*-2-Aminocyclohexanol

12. Acidity of Thiols (Section 8.6A)
Thiols are weak acids, pK_a 8–9, but are considerably stronger acids than alcohols, pK_a 16–18.

$$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+ \quad pK_a = 8.5$$

13. Oxidation to Disulfides (Section 8.6B)
Oxidation of a thiol by O_2 gives a disulfide:

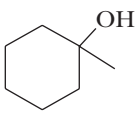
$$2\ RSH + \tfrac{1}{2}O_2 \longrightarrow RS\text{-}SR + H_2O$$

PROBLEMS

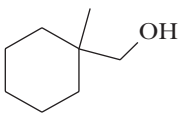
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

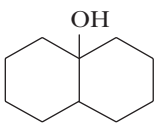
Structure and Nomenclature

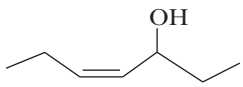
8.13 Classify the alcohols as primary, secondary, or tertiary. **(See Example 8.2)**

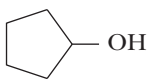
(a) 

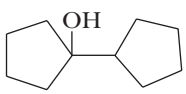
(b) $(CH_3)_3COH$

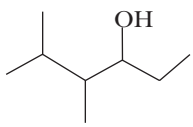
(c) 

(d) 

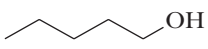
(e) 

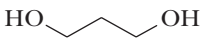
(f) 

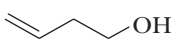
(g) 

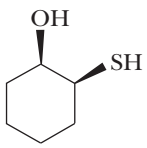
(h) 

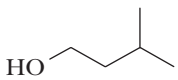
8.14 Provide an IUPAC or common name for these compounds: **(See Examples 8.1, 8.3, 8.11)**

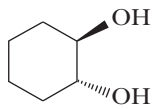
(a) 

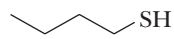
(b) 

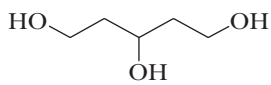
(c) 

(d) 

(e) 

(f) 

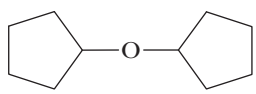
(g) 

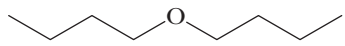
(h) 

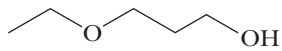
8.15 Draw a structural formula for each alcohol: **(See Examples 8.1, 8.3, 8.11)**

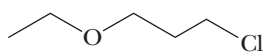
(a) Isopropyl alcohol
(b) Propylene glycol
(c) (*R*)-5-Methyl-2-hexanol
(d) 2-Methyl-2-propyl-1,3-propanediol
(e) 2,2-Dimethyl-1-propanol
(f) 2-Mercaptoethanol
(g) 1,4-Butanediol
(h) (*Z*)-5-Methyl-2-hexen-1-ol
(i) *cis*-3-Penten-1-ol
(j) *trans*-1,4-Cyclohexanediol

8.16 Write names for these ethers: **(See Example 8.7)**

(a) 

(b) 

(c) 

(d) 

8.17 Name and draw structural formulas for the eight isomeric alcohols with the molecular formula $C_5H_{12}O$. Which are chiral? **(See Examples 8.1, 8.3)**

Physical Properties

8.18 Arrange these compounds in order of increasing boiling point (values in °C are –42, 78, 117, and 198):

(a) $CH_3CH_2CH_2CH_2OH$ (c) $HOCH_2CH_2OH$

(b) CH_3CH_2OH (d) $CH_3CH_2CH_3$

8.19 Arrange these compounds in order of increasing boiling point (values in °C are –42, –24, 78, and 118):

(a) CH_3CH_2OH (c) $CH_3CH_2CH_3$

(b) CH_3OCH_3 (d) CH_3COOH

8.20 Propanoic acid and methyl acetate are constitutional isomers, and both are liquids at room temperature:

Propanoic acid Methyl acetate

One of these compounds has a boiling point of 141 °C; the other has a boiling point of 57 °C. Which compound has which boiling point?

8.21 Draw all possible staggered conformations of ethylene glycol ($HOCH_2CH_2OH$). Can you explain why the conformation in which the —OH groups are closest to each other is more stable than the conformation in which the —OH groups are farthest apart by approximately 4.2 kJ/mol (1 kcal/mol)? **(See Example 3.7)**

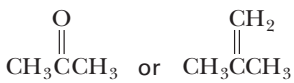
8.22 Following are structural formulas for 1-butanol and 1-butanethiol:

1-Butanol 1-Butanethiol

One of these compounds has a boiling point of 98.5 °C; the other has a boiling point of 117 °C. Which compound has which boiling point?

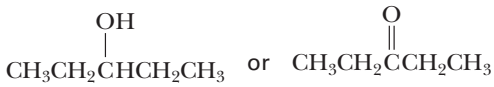
8.23 From each pair of compounds, select the one that is more soluble in water: **(See Example 8.8)**

(a) CH_2Cl_2 or CH_3OH

(b) CH_3CCH_3 (O) or CH_3CCH_3 (CH_2) 

(c) CH_3CH_2Cl or $NaCl$

(d) $CH_3CH_2CH_2SH$ or $CH_3CH_2CH_2OH$

(e) $CH_3CH_2CHCH_2CH_3$ (OH) or $CH_3CH_2CCH_2CH_3$ (O) 

8.24 Arrange the compounds in each set in order of decreasing solubility in water: **(See Example 8.8)**

(a) Ethanol; butane; diethyl ether

(b) 1-Hexanol; 1,2-hexanediol; hexane

8.25 Each of the following compounds is a common organic solvent. From each pair of compounds, select the solvent with the greater solubility in water. **(See Example 8.8)**

(a) CH_2Cl_2 or CH_3CH_2OH

(b) $CH_3CH_2OCH_2CH_3$ or CH_3CH_2OH

(c) CH_3CCH_3 (O) or $CH_3CH_2OCH_2CH_3$ 

(d) $CH_3CH_2OCH_2CH_3$ or $CH_3(CH_2)_3CH_3$

Synthesis of Alcohols

8.26 Give the structural formula of an alkene or alkenes from which each alcohol or glycol can be prepared: **(See Examples 5.5, 8.10)**

(a) 2-Butanol (d) 2-Methyl-2-pentanol

(b) 1-Methylcyclohexanol (e) Cyclopentanol

(c) 3-Hexanol (f) 1,2-Propanediol

8.27 The addition of bromine to cyclopentene and the acid-catalyzed hydrolysis of cyclopentene oxide are both stereoselective; each gives a *trans* product. Compare the mechanisms of these two reactions, and show how each mechanism accounts for the formation of the *trans* product.

Acidity of Alcohols and Thiols

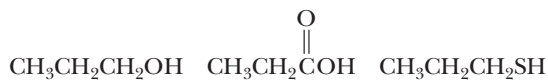
8.28 From each pair, select the stronger acid, and, for each stronger acid, write a structural formula for its conjugate base: **(See Examples 8.4, 8.12)**

(a) H_2O or H_2CO_3

(b) CH_3OH or CH_3COOH

(c) CH_3COOH or CH_3CH_2SH

8.29 Arrange these compounds in order of increasing acidity (from weakest to strongest): **(See Examples 8.4, 8.12)**



8.30 From each pair, select the stronger base, and, for each stronger base, write the structural formula of its conjugate acid: **(See Examples 8.4, 8.12)**

(a) OH^- or CH_3O^-

(b) $CH_3CH_2S^-$ or $CH_3CH_2O^-$

(c) $CH_3CH_2O^-$ or NH_2^-

8.31 Label the stronger acid, stronger base, weaker acid, and weaker base in each of the following equilibria, and then predict the position of each equilibrium (for pK_a values, see Table 2.2): **(See Example 8.4)**

(a) $CH_3CH_2O^- + HCl \rightleftharpoons CH_3CH_2OH + Cl^-$

(b) CH_3COH (O) $+ CH_3CH_2O^- \rightleftharpoons CH_3CO^-$ (O) $+ CH_3CH_2OH$ 

8.32 Predict the position of equilibrium for each acid–base reaction; that is, does each lie considerably to the left, does each lie considerably to the right, or are the concentrations evenly balanced? **(See Examples 8.4, 8.12)**

(a) $CH_3CH_2OH + Na^+OH^- \rightleftharpoons CH_3CH_2O^-Na^+ + H_2O$

(b) $CH_3CH_2SH + Na^+OH^- \rightleftharpoons CH_3CH_2S^-Na^+ + H_2O$

(c) $CH_3CH_2OH + CH_3CH_2S^-Na^+ \rightleftharpoons CH_3CH_2O^-Na^+ + CH_3CH_2SH$

(d) $CH_3CH_2S^-\ Na^+ + CH_3\overset{\overset{O}{\|}}{C}OH \rightleftharpoons CH_3CH_2SH + CH_3\overset{\overset{O}{\|}}{C}O^-\ Na^+$

Reactions of Alcohols

8.33 Show how to distinguish between cyclohexanol and cyclohexene by a simple chemical test. (*Hint*: Treat each with Br_2 in CCl_4 and watch what happens.)

8.34 Write equations for the reaction of 1-butanol, a primary alcohol, with these reagents: **(See Examples 8.4, 8.6)**

(a) Na metal

(b) HBr, heat

(c) $K_2Cr_2O_7$, H_2SO_4, heat

(d) $SOCl_2$

(e) Pyridinium chlorochromate (PCC)

8.35 Write equations for the reaction of 2-butanol, a secondary alcohol, with these reagents: **(See Examples 8.4, 8.6)**

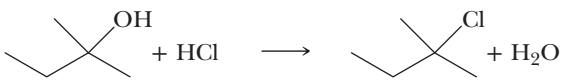
(a) Na metal (b) H_2SO_4, heat

(c) HBr, heat (d) $K_2Cr_2O_7$, H_2SO_2, heat

(e) $SOCl_2$ (f) Pyridinium chlorochromate (PCC)

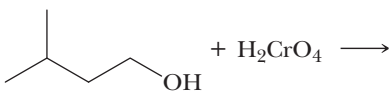
8.36 When (*R*)-2-butanol is left standing in aqueous acid, it slowly loses its optical activity. When the organic material is recovered from the aqueous solution, only 2-butanol is found. Account for the observed loss of optical activity.

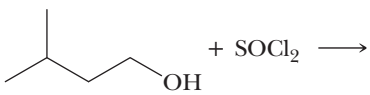
8.37 What is the most likely mechanism of the following reaction?



Draw a structural formula for the intermediate(s) formed during the reaction.

8.38 Complete the equations for these reactions: **(See Examples 8.6, 8.9)**

(a)


(b)


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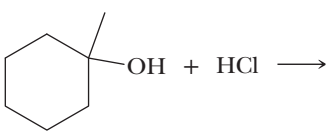

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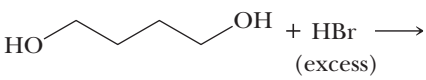

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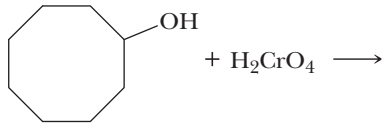

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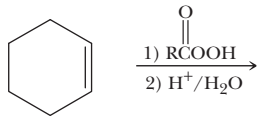
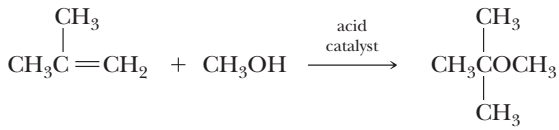
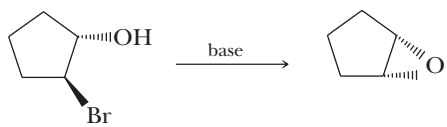


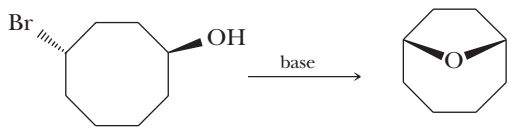
***8.39** In the commercial synthesis of methyl *tert*-butyl ether (MTBE), once used as an antiknock, octane-improving gasoline additive, 2-methylpropene and methanol are passed over an acid catalyst to give the ether. Propose a mechanism for this reaction. **(See Examples 5.5, 5.6)**

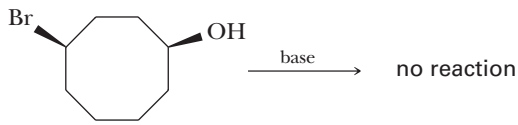


2-Methylpropene (Isobutylene) Methanol 2-Methoxy-2-methylpropane (Methyl-tert-butyl ether, MTBE)

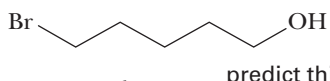
8.40 Cyclic bromoalcohols, upon treatment with base, can sometimes undergo intramolecular S_N2 reactions to form the ethers shown in reactions (a) and (b). Provide a mechanism for reactions (a) and (b). Indicate why equation (c) does not yield a similar reaction.

(a)


(b)


(c)


no reaction

(d)


predict this product and provide a mechanism for its formation

Syntheses

8.41 Show how to convert **(See Examples 8.5, 8.6, 8.10)**

(a) 1-Propanol to 2-propanol in two steps.

(b) Cyclohexene to cyclohexanone in two steps.

(c) Cyclohexanol to *trans*-1,2-cyclohexanediol in three steps.

(d) Propene to propanone (acetone) in two steps.

8.42 Show how to convert cyclohexanol to these compounds: **(See Examples 8.5, 8.6)**

(a) Cyclohexene
(b) Cyclohexane
(c) Cyclohexanone
(d) Cylohexene oxide

8.43 Show reagents and experimental conditions that can be used to synthesize these compounds from 1-propanol (any derivative of 1-propanol prepared in an earlier part of this problem may be used for a later synthesis): **(See Examples 8.5, 8.6, 8.9, 8.10)**

(a) Propanal
(b) Propanoic acid
(c) Propene
(d) 2-Propanol
(e) 2-Bromopropane
(f) 1-Chloropropane
(g) Propanone
(h) 1,2-Propanediol

8.44 Show how to prepare each compound from 2-methyl-1-propanol (isobutyl alcohol). For any preparation involving more than one step, show each intermediate compound formed. **(See Examples 8.5, 8.6, 8.9, 8.10)**

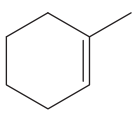
(a) $CH_3C(CH_3)=CH_2$

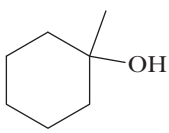
(b) $CH_3C(CH_3)(OH)CH_3$

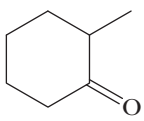
(c) $CH_3C(CH_3)(HO)CH_2OH$

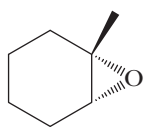
(d) $CH_3CH(CH_3)COOH$

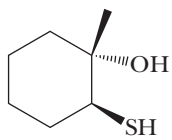
8.45 Show how to prepare each compound from 2-methylcyclohexanol: **(See Examples 8.5, 8.6, 8.9, 8.10)**

(a) 

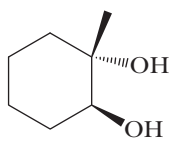
(b) 

(c) 

(d) 

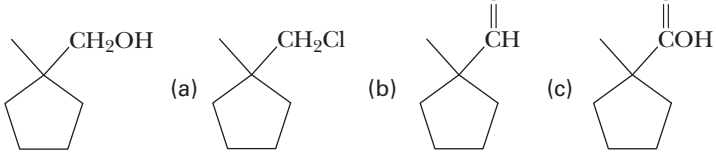
(e) 

racemic

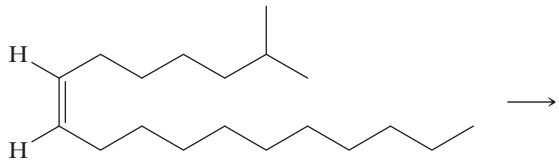
(f) 

For any preparation involving more than one step, show each intermediate compound formed.

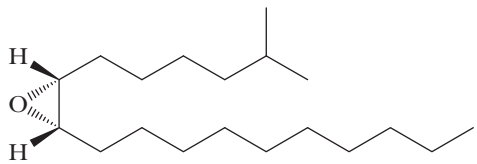
8.46 Show how to convert the alcohol on the left to compounds (a), (b), and (c). **(See Example 8.5)**



***8.47** Disparlure, a sex attractant of the gypsy moth (*Porthetria dispar*), has been synthesized in the laboratory from the following (*Z*)-alkene: **(See Example 8.9)**



(*Z*)-2-Methyl-7-octadecene



Disparlure

© Marek Swadzba/Stockphoto

Gypsy moth caterpillar.

(a) How might the (*Z*)-alkene be converted to disparlure?
(b) How many stereoisomers are possible for disparlure? How many are formed in the sequence you chose?

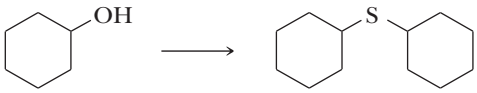
***8.48** The chemical name for bombykol, the sex pheromone secreted by the female silkworm moth to attract male silkworm moths, is *trans*-10-*cis*-12-hexadecadien-1-ol. (The compound has one hydroxyl group and two carbon–carbon double bonds in a 16-carbon chain.)

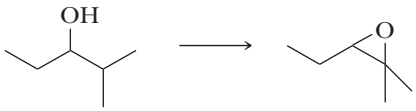
(a) Draw a structural formula for bombykol, showing the correct configuration about each carbon–carbon double bond.
(b) How many *cis–trans* isomers are possible for the structural formula you drew in part (a)? All possible *cis–trans* isomers have been synthesized in the laboratory, but only the one named bombykol is produced by the female silkworm moth, and only it attracts male silkworm moths.

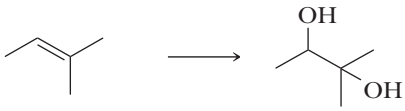
CHEMICAL TRANSFORMATIONS

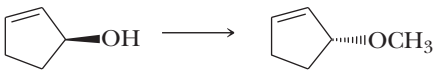
8.49 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.*

(a) 

(b) 

(c) 

(d) 

(e) 

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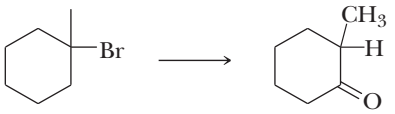
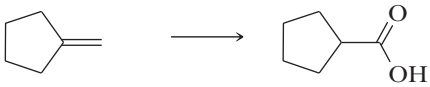
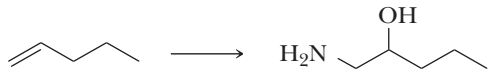
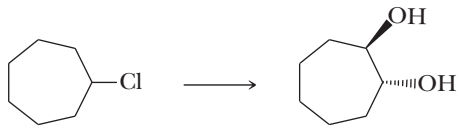
(g) 

(h) 

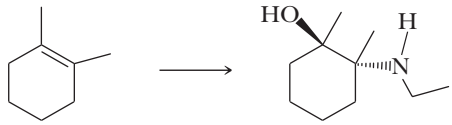
(i) 

(j) 

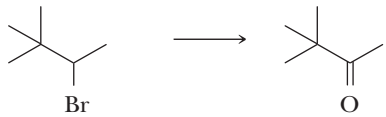
(k) 

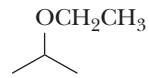
(l) 

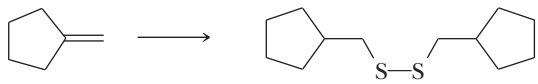
racemic

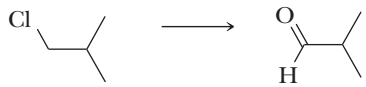
(m) 

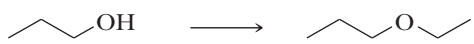
racemic

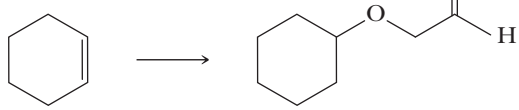
(n) 

(o) $HOCH_2CH_3$ 

(p) 

(q) 

(r) 

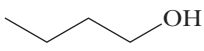
(s) 

LOOKING AHEAD

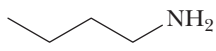
8.50 Compounds that contain an N—H group associate by hydrogen bonding.

(a) Do you expect this association to be stronger or weaker than that between compounds containing an O—H group?

(b) Based on your answer to part (a), which would you predict to have the higher boiling point, 1-butanol or 1-butanamine?

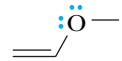


1-Butanol

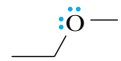


1-Butanamine

8.51 Draw a resonance structure for methyl vinyl ether in which the oxygen is positively charged. Compared with ethyl methyl ether, how does the resonance structure for methyl vinyl ether influence the reactivity of its oxygen toward an electrophile?

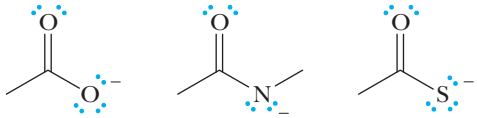


Methyl vinyl ether



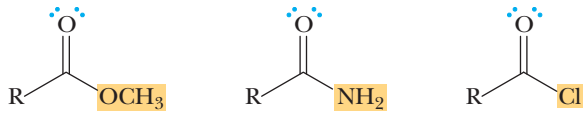
Ethyl methyl ether

8.52 Rank the members in each set of reagents from most to least nucleophilic:

(a) 

(b) 

8.53 In Chapter 14 we will see that the reactivity of the following carbonyl compounds is directly proportional to the stability of the leaving group. Rank the order of reactivity of these carbonyl compounds from most reactive to least reactive based on the stability of the leaving group.



A B C

GROUP LEARNING ACTIVITIES

8.54 Discuss why primary alcohols (with the exception of ethanol) cannot be prepared by the acid-catalyzed hydration of alkenes. You'll want to discuss the mechanism of acid-catalyzed hydration and consider the reactive species involved.

8.55 Discuss why sodium hydroxide is not a good reagent for the synthesis of alkoxides from alcohols. Similarly, could sodium hydroxide be used to synthesize alkylsulfides from thiols? Why or why not? You'll want to discuss the type of reactions that would occur in both reactions as well as what makes a reaction synthetically useful.

8.56 One of the following alcohols is used to de-ice airplanes during extreme cold weather. As a group, decide which of the three alcohols would be most suitable for the job by discussing factors that one must consider for such an application.

CH_3OH	CH_3CH_2OH	$(CH_3)_3COH$
Methanol	Ethanol	*tert*-Butanol

***8.57** Shown is the structure of Erythromycin A, an important antibiotic that is used to treat a number of bacterial infections. In your study group,

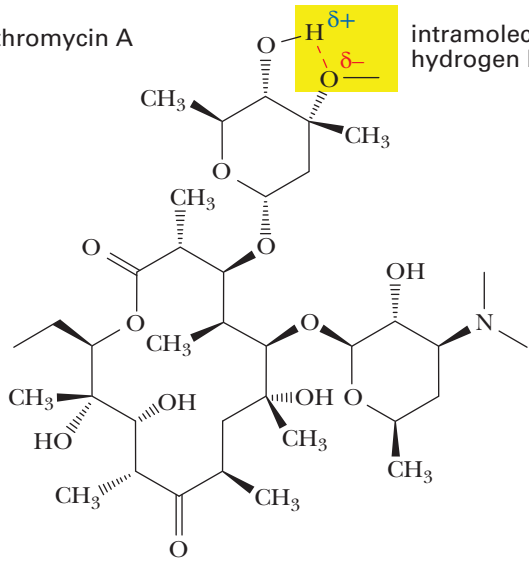
(a) Locate all the hydroxyl groups in Erythromycin A and classify each as 1°, 2°, 3°.

(b) Four of these hydroxyl groups are involved in intramolecular hydrogen bonding. One of these is pointed out on the structural formula and it creates a five-membered ring. Locate the other three alcohols that have the potential for intramolecular hydrogen bonding. Note that nitrogen can also form hydrogen bonds.

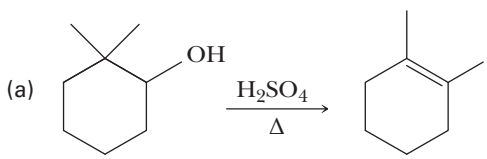
(c) Identify the other functional groups in Erythromycin A.

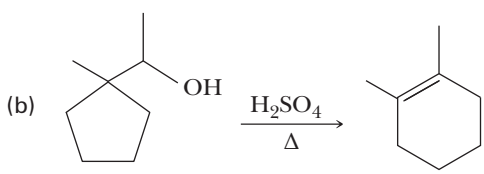
(d) Locate all of the stereocenters, determine their R/S configuration, predict the maximum number of stereoisomers possible for Erythromycin A.

Erythromycin A

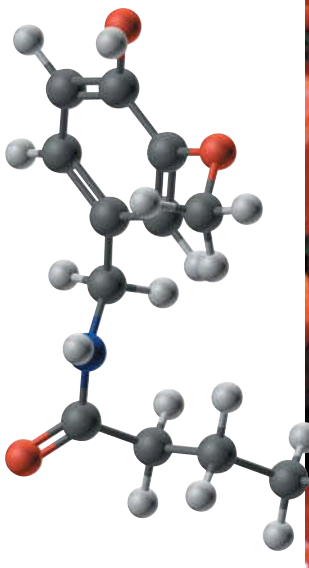


8.58 Practice your arrow pushing skills by proposing mechanisms for the following reations:

(a) 

(b) 

Benzene and Its Derivatives



9

Peppers of the capsicum family. Hot peppers contain significant amounts of the chemical capsaicin, which is used for medicinal purposes as well as for tantalizing taste buds (see Chemical Connections, "Capsaicin, for Those Who Like It Hot"). Inset: A model of capsaicin.

Courtesy Douglas Brown

BENZENE, A COLORLESS LIQUID, was first isolated by Michael Faraday in 1825 from the oily residue that collected in the illuminating gas lines of London. Benzene's molecular formula, C_6H_6, suggests a high degree of unsaturation. For comparison, an alkane with six carbons has a molecular formula of C_6H_{14}, and a cycloalkane with six carbons has a molecular formula of C_6H_{12}. Considering benzene's high degree of unsaturation, it might be expected to show many of the reactions characteristic of alkenes. Yet, benzene is remarkably *un*reactive! It does not undergo the addition, oxidation, and reduction reactions characteristic of alkenes. For example, benzene does not react with bromine, hydrogen chloride, or other reagents that usually add to carbon–carbon double bonds. Nor is benzene oxidized by peracids under conditions that readily oxidize alkenes. When benzene reacts, it does so by substitution in which a hydrogen atom is replaced by another atom or a group of atoms.

The term *aromatic* was originally used to classify benzene and its derivatives because many of them have distinctive odors. It became clear, however, that a sounder classification for these compounds would be one based on structure and chemical reactivity, not aroma. As it is now used, the term **aromatic** refers instead to the fact that benzene and its derivatives are highly unsaturated compounds that are unexpectedly stable toward reagents that react with alkenes.

Aromatic compound A term used to classify benzene and its derivatives.

We use the term **arene** to describe aromatic hydrocarbons, by analogy with alkane and alkene. Benzene is the parent arene. Just as we call a group derived by the removal of an H from an alkane an alkyl group and give it the symbol R—, we call a group derived by the removal of an H from an arene an **aryl group** and give it the symbol **Ar**—.

Arene An aromatic hydrocarbon.

Aryl group A group derived from an aromatic compound (an arene) by the removal of an H; given the symbol Ar—.

Ar— The symbol used for an aryl group, by analogy with R— for an alkyl group.

9.1 What Is the Structure of Benzene?

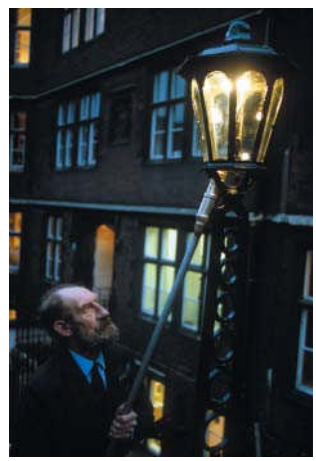
Let us imagine ourselves in the mid-nineteenth century and examine the evidence on which chemists attempted to build a model for the structure of benzene. First, because the molecular formula of benzene is C_6H_6, it seemed clear that the molecule must be highly unsaturated. Yet benzene does not show the chemical properties of alkenes, the only unsaturated hydrocarbons known at that time. Benzene does undergo chemical reactions, but its characteristic reaction is substitution rather than addition. When benzene is treated with bromine in the presence of ferric chloride as a catalyst, for example, only one compound with the molecular formula C_6H_5Br forms:

$$\underset{\text{Benzene}}{C_6H_6} + Br_2 \xrightarrow{FeCl_3} \underset{\text{Bromobenzene}}{C_6H_5Br} + HBr$$

Chemists concluded, therefore, that all six carbons and all six hydrogens of benzene must be equivalent. When bromobenzene is treated with bromine in the presence of ferric chloride, three isomeric dibromobenzenes are formed:

$$\underset{\text{Bromobenzene}}{C_6H_5Br} + Br_2 \xrightarrow{FeCl_3} \underset{\substack{\text{Dibromobenzene}\\ \text{(formed as a mixture of}\\ \text{three constitutional isomers)}}}{C_6H_4Br_2} + HBr$$

For chemists in the mid-nineteenth century, the problem was to incorporate these observations, along with the accepted tetravalence of carbon, into a structural formula for benzene. Before we examine their proposals, we should note that the problem of the structure of benzene and other aromatic hydrocarbons has occupied the efforts of chemists for over a century. It was not until the 1930s that chemists developed a general understanding of the unique structure and chemical properties of benzene and its derivatives.

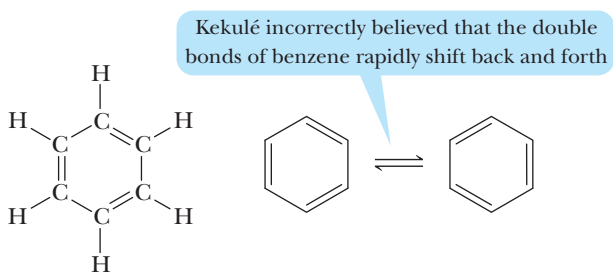


© Presselect/Alamy Stock Photo

Gas lamps like this were the original source of Faraday's discovery of benzene.

A. Kekulé's Model of Benzene

The first structure for benzene, proposed by August Kekulé in 1872, consisted of a six-membered ring with alternating single and double bonds and with one hydrogen bonded to each carbon. Kekulé further proposed that the ring contains three double bonds that shift back and forth so rapidly that the two forms cannot be separated. Each structure has become known as a **Kekulé structure**.



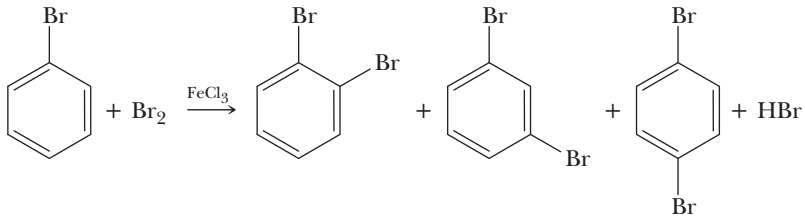
A Kekulé structure, showing all atoms

Kekulé structures as line-angle formulas

Because all of the carbons and hydrogens of Kekulé's structure are equivalent, substituting bromine for any one of the hydrogens gives the same compound. Thus,

Kekulé's proposed structure was consistent with the fact that treating benzene with bromine in the presence of ferric chloride gives only one compound with the molecular formula C_6H_5Br.

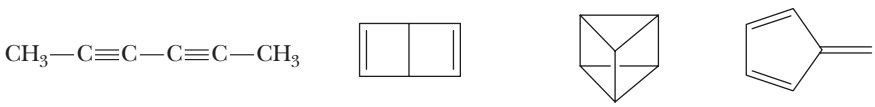
His proposal also accounted for the fact that the bromination of bromobenzene gives three (and only three) isomeric dibromobenzenes:



The three isomeric dibromobenzenes

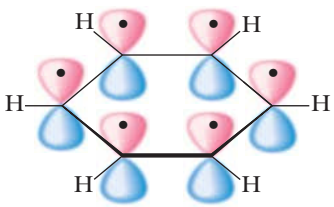
Although Kekulé's proposal was consistent with many experimental observations, it was contested for years. The major objection was that it did not account for the unusual chemical behavior of benzene. If benzene contains three double bonds, why, his critics asked, doesn't it show the reactions typical of alkenes? Why doesn't it add three moles of bromine to form 1,2,3,4,5,6-hexabromocyclohexane? Why, instead, does benzene react by substitution rather than addition?

Following are four structures that were also considered for the structure of benzene.

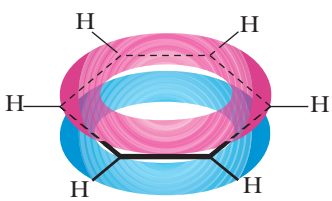


Hexa-2,4-diyne "Dewar" benzene Prismane Fulvene

Which of these would not show the typical reactions of alkenes? Which would give only one possible product when bromine is substituted for a hydrogen? Which of these would show a high degree of strain due to bond angle or bond length?



(a)

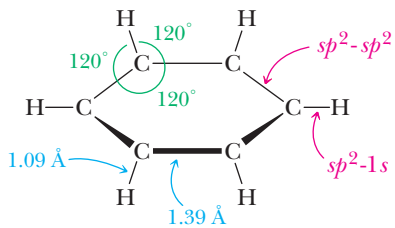


(b)

FIGURE 9.1 Orbital overlap model of the bonding in benzene. (a) The carbon, hydrogen framework. The six 2*p* orbitals, each with one electron, are shown uncombined. (b) The overlap of parallel 2*p* orbitals forms a continuous pi cloud, shown by one torus above the plane of the ring and a second below the plane of the ring.

B. The Orbital Overlap Model of Benzene

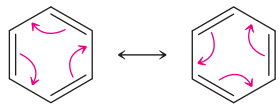
The concepts of the **hybridization of atomic orbitals** and the **theory of resonance**, developed by Linus Pauling in the 1930s, provided the first adequate description of the structure of benzene. The carbon skeleton of benzene forms a regular hexagon with C—C—C and H—C—C bond angles of 120°. For this type of bonding, carbon uses sp^2 hybrid orbitals (Section 1.6E). Each carbon forms sigma bonds to two adjacent carbons by the overlap of sp^2–sp^2 hybrid orbitals and one sigma bond to hydrogen by the overlap of sp^2–1*s* orbitals. As determined experimentally, all carbon–carbon bonds in benzene are the same length, 1.39 Å, a value almost midway between the length of a single bond between sp^3 hybridized carbons (1.54 Å) and that of a double bond between sp^2 hybridized carbons (1.33 Å):



Each carbon also has a single unhybridized 2*p* orbital that contains one electron. These six 2*p* orbitals lie perpendicular to the plane of the ring and overlap to form a continuous pi cloud encompassing all six carbons. The electron density of the pi system of a benzene ring lies in one torus (a doughnut-shaped region) above the plane of the ring and a second torus below the plane (Figure 9.1).

C. The Resonance Model of Benzene

One of the postulates of resonance theory is that, if we can represent a molecule or ion by two or more contributing structures, then that molecule cannot be adequately represented by any single contributing structure. We represent benzene as a hybrid of two equivalent contributing structures, often referred to as *Kekulé structures*:



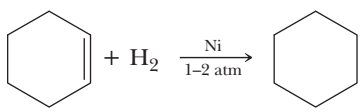
Benzene as a hybrid of two equivalent contributing structures

Each Kekulé structure makes an equal contribution to the hybrid; thus, the C—C bonds are neither single nor double bonds, but something intermediate. We recognize that neither of these contributing structures exists (they are merely alternative ways to pair $2p$ orbitals with no reason to prefer one over the other) and that the actual structure is a superposition of both. Nevertheless, chemists continue to use a single contributing structure to represent this molecule because it is as close as we can come to an accurate structure within the limitations of classical Lewis structures and the tetravalence of carbon.

D. The Resonance Energy of Benzene

Resonance energy The difference in energy between a resonance hybrid and the most stable of its hypothetical contributing structures.

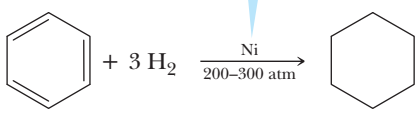
Resonance energy is the difference in energy between a resonance hybrid and its most stable hypothetical contributing structure. One way to estimate the resonance energy of benzene is to compare the heats of hydrogenation of cyclohexene and benzene (benzene can be made to undergo hydrogenation under extreme conditions). In the presence of a transition metal catalyst, hydrogen readily reduces cyclohexene to cyclohexane (Section 5.6):



$\Delta H^0 = -120$ kJ/mol (−28.6 kcal/mol)

By contrast, benzene is reduced only very slowly to cyclohexane under these conditions. It is reduced more rapidly when heated and under a pressure of several hundred atmospheres of hydrogen:

because benzene does not react readily with reagents that add to alkenes, hydrogenation of benzene must be performed at extremely high pressures



$\Delta H^0 = -209$ kJ/mol (−49.8 kcal/mol)

The catalytic reduction of an alkene is an exothermic reaction (Section 5.6). The heat of hydrogenation per double bond varies somewhat with the degree of substitution of the double bond; for cyclohexene $\Delta H^0 = -120$ kJ/mol (−28.6 kcal/mol). If we imagine benzene in which the $2p$ electrons do not overlap outside of their original C—C double bonds, a hypothetical compound with alternating single and double bonds, we might expect its heat of hydrogenation to be $3 \times -120 = -360$ kJ/mol(−86.0 kcal/mol. Instead, the heat of hydrogenation of benzene is only −209 kJ/mol(−49.8 kcal/mol). The difference of 151 kJ/mol (36.1 kcal/mol) between the expected value and the experimentally observed value is the **resonance energy of benzene**. Figure 9.2 shows these experimental results in the form of a graph.

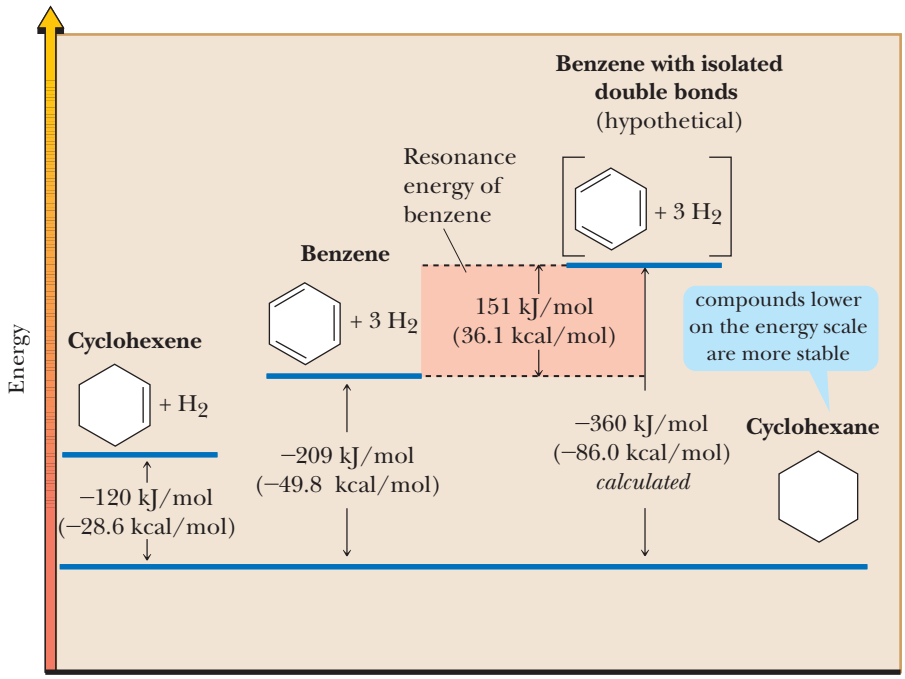
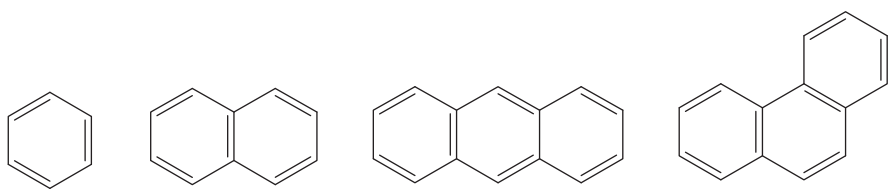


FIGURE 9.2 The resonance energy of benzene, as determined by a comparison of the heats of hydrogenation of cyclohexene, benzene, and the hypothetical benzene.

For comparison, the strength of a carbon–carbon single bond is approximately 333–418 kJ/mol (80–100 kcal/mol), and that of hydrogen bonding in water and low-molecular-weight alcohols is approximately 8.4–21 kJ/mol (2–5 kcal/mol). Thus, although the resonance energy of benzene is less than the strength of a carbon–carbon single bond, it is considerably greater than the strength of hydrogen bonding in water and alcohols. In Section 8.1C, we saw that hydrogen bonding has a dramatic effect on the physical properties of alcohols compared with those of alkanes. In this chapter, we see that the resonance energy of benzene and other aromatic hydrocarbons has a dramatic effect on their chemical reactivity.

Following are resonance energies for benzene and several other aromatic hydrocarbons:



	Benzene	Naphthalene	Anthracene	Phenanthrene
Resonance energy [kJ/mol (kcal/mol)]	150 (35.8)	255 (60.9)	347 (82.9)	381 (91.0)

9.2 What Is Aromaticity?

Many other types of molecules besides benzene and its derivatives show aromatic character; that is, they contain high degrees of unsaturation, yet fail to undergo characteristic alkene addition and oxidation–reduction reactions. What chemists had long sought to understand were the principles underlying aromatic character. The German chemical physicist Erich Hückel solved this problem in the 1930s.

Hückel's criteria are summarized as follows. To be aromatic, a ring must

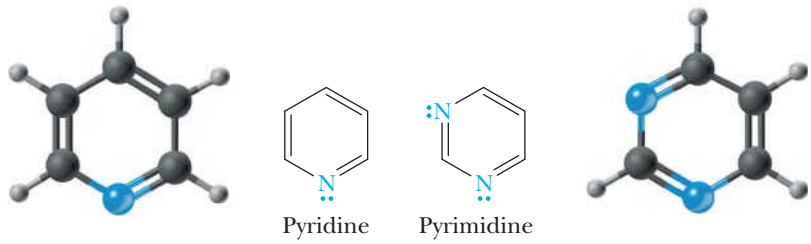
1. Have one $2p$ orbital on each of its atoms.
2. Be planar or nearly planar, so that there is continuous overlap or nearly continuous overlap of all $2p$ orbitals of the ring.
3. Have 2, 6, 10, 14, 18, or so forth pi electrons in the cyclic arrangement of $2p$ orbitals.

this criterion is also called the **$4n + 2$ rule** because the allowable numbers of pi electrons can be determined when n is substituted by any integer, including zero

Benzene meets these criteria. It is cyclic, planar, has one 2*p* orbital on each carbon atom of the ring, and has 6 pi electrons (an aromatic sextet) in the cyclic arrangement of its 2*p* orbitals.

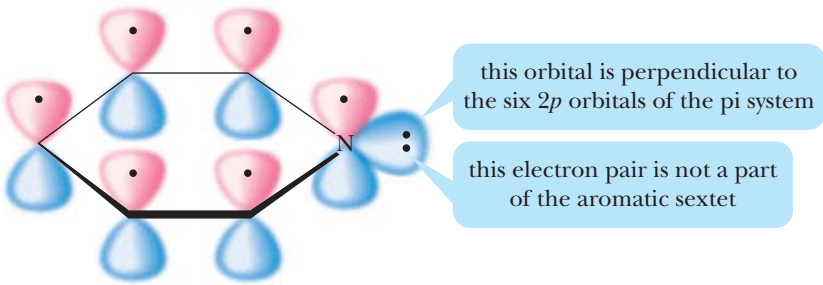
Let us apply these criteria to several **heterocyclic compounds**, all of which are aromatic. Pyridine and pyrimidine are heterocyclic analogs of benzene. In pyridine, one CH group of benzene is replaced by a nitrogen atom, and in pyrimidine, two CH groups are replaced by nitrogen atoms:

Heterocyclic compounds An organic compound that contains one or more atoms other than carbon in its ring.



Pyridine Pyrimidine

Each molecule meets the Hückel criteria for aromaticity: Each is cyclic and planar, has one 2*p* orbital on each atom of the ring, and has six electrons in the pi system. In pyridine, nitrogen is sp^2 hybridized, and its unshared pair of electrons occupies an sp^2 orbital perpendicular to the 2*p* orbitals of the pi system and thus is not a part of the pi system. In pyrimidine, neither unshared pair of electrons of nitrogen is part of the pi system. The resonance energy of pyridine is 134 kJ/mol (32.0 kcal/mol), slightly less than that of benzene. The resonance energy of pyrimidine is 109 kJ/mol (26.0 kcal/mol).

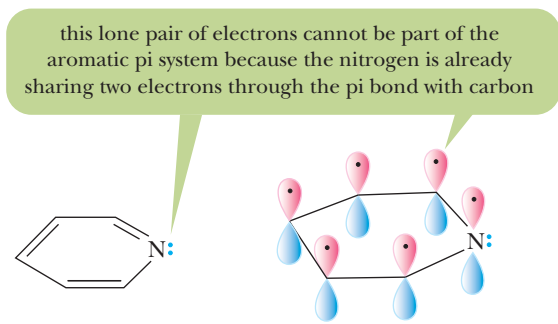


Pyridine

Determine Whether a Lone Pair of Electrons Is or Is Not Part of an Aromatic Pi System

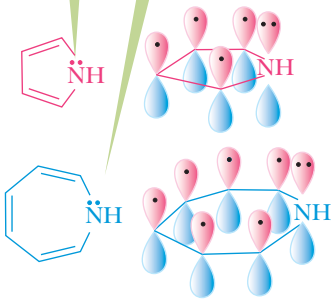
HOW TO 9.1

(a) First, determine whether the atom containing the lone pair of electrons is part of a double bond. If it is part of a double bond, it is not possible for the lone pair to be part of the aromatic pi system.



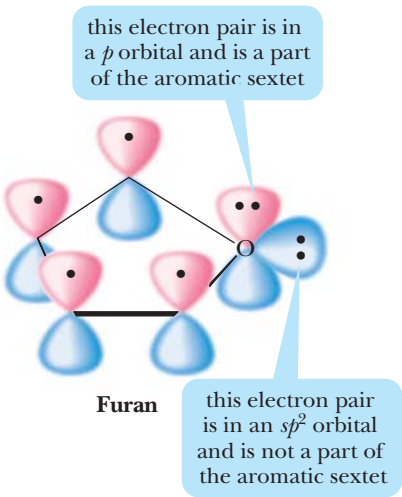
(b) If the atom containing the lone pair of electrons is not part of a double bond, it is possible for the lone pair of electrons to be part of the pi system. Determine this by placing the atom in a hybridization state that places the lone pair of electrons in a *p* orbital. If this increases the number of aromatic pi electrons to either 2, 6, 10, 14, and so on, then the lone pair of electrons is part of the pi aromatic system. If placing the lone pair of electrons in the pi system changes the total number of pi electrons to any other number (e.g., 3–5, 7–9, etc.), the lone pair is not part of the aromatic pi system.

a nitrogen atom with three single bonds is normally sp^3 hybridized. However, to determine if the lone pair of electrons belongs in the pi system, we must change the hybridization of nitrogen to sp^2 so that the electrons can reside in a p orbital

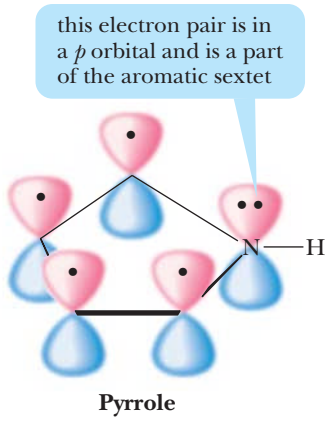


The lone pair on nitrogen gives the pi system six electrons. Therefore, the nitrogen should be sp^2 hybridized.

The lone pair gives the pi system eight electrons. Therefore, the nitrogen should not be sp^2 hybridized.



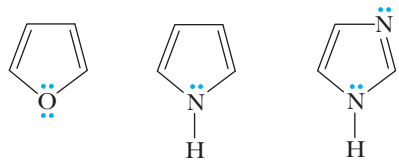
Furan



Pyrrole

FIGURE 9.3 Origin of the six pi electrons (the aromatic sextet) in furan and pyrrole. The resonance energy of furan is 67 kJ/mol (16 kcal/mol); that of pyrrole is 88 kJ/mol (21 kcal/mol).

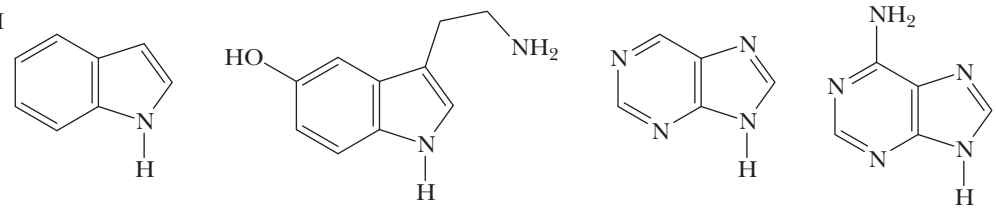
The five-membered-ring compounds furan, pyrrole, and imidazole are also aromatic:



Furan Pyrrole Imidazole

In these planar compounds, each heteroatom is sp^2 hybridized, and its unhybridized $2p$ orbital is part of a continuous cycle of five $2p$ orbitals. In furan, one unshared pair of electrons of the heteroatom lies in the unhybridized $2p$ orbital and is a part of the pi system (Figure 9.3). The other unshared pair of electrons lies in an sp^2 hybrid orbital, perpendicular to the $2p$ orbitals, and is not a part of the pi system. In pyrrole, the unshared pair of electrons on nitrogen is part of the aromatic sextet. In imidazole, the unshared pair of electrons on one nitrogen is part of the aromatic sextet; the unshared pair on the other nitrogen is not.

Nature abounds with compounds having a heterocyclic aromatic ring fused to one or more other rings. Two such compounds especially important in the biological world are indole and purine:

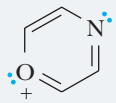


Indole Serotonin (a neurotransmitter) Purine Adenine

Indole contains a pyrrole ring fused with a benzene ring. Compounds derived from indole include the amino acid L-tryptophan (Section 18.2C) and the neurotransmitter serotonin. Purine contains a six-membered pyrimidine ring fused with a five-membered imidazole ring. Adenine is one of the building blocks of deoxyribonucleic acids (DNA) and ribonucleic acids (RNA), as described in Chapter 20. It is also a component of the biological oxidizing agent nicotinamide adenine dinucleotide, abbreviated NAD^+ (Section 21.1B).

EXAMPLE 9.1

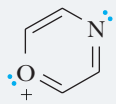
Which of the following compounds are aromatic?

(a) 
(b) 
(c) 

STRATEGY

Determine whether each atom of the ring contains a 2*p* orbital and whether the molecule is planar. If these criteria are met, determine the number of pi electrons. Those having 2, 6, 10, 14, and so on electrons are aromatic.

SOLUTION

(a) 

This molecule is planar, and each atom of the ring contains a 2*p* orbital. There is a total of 6 pi electrons. The molecule is aromatic.

(b) 

This molecule is planar, and each atom of the ring contains a 2*p* orbital. There is a total of 4 pi electrons. The molecule is not aromatic.

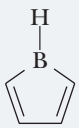
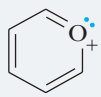
(c) 

Treat the molecule as planar for the purposes of determining aromaticity. Also, treat each carbon atom in the ring as containing a 2*p* orbital. That is, treat the oxygen atom as sp^2 hybridized, so that one of its lone pairs of electrons will enter the pi electron system (if we do not do this, the molecule cannot be aromatic because an oxygen atom with two lone pairs of electrons and two single bonds is normally sp^3 hybridized). Despite these special considerations, the molecule ends up with a total of eight pi electrons, so the molecule is not aromatic. Because it is not aromatic, the oxygen has no driving force to be sp^2 hybridized and is, in fact, sp^3 hybridized. Also, the molecule has no driving force to be planar, and in fact, the molecule is nonplanar.

See problem 9.11

PROBLEM 9.1

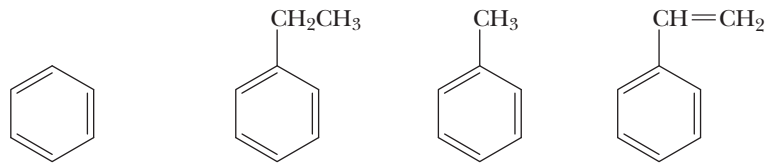
Which of the following compounds are aromatic?

(a) 
(b) 
(c) 
(d) 

9.3 How Are Benzene Compounds Named, and What Are Their Physical Properties?

A. Monosubstituted Benzenes

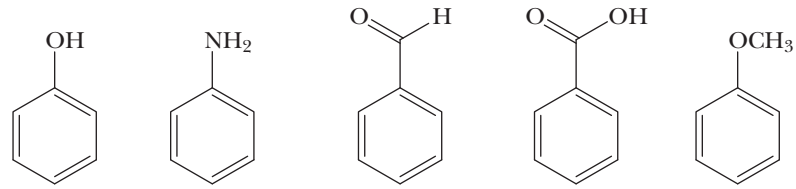
Monosubstituted alkylbenzenes are named as derivatives of benzene; an example is ethylbenzene. The IUPAC system retains certain common names for several of the simpler monosubstituted alkylbenzenes. Examples are **toluene** (rather than methylbenzene) and **styrene** (rather than phenylethylene):



	Benzene	Ethylbenzene	Toluene	Styrene
mp (°C)	5.5	−95	−93	−31
bp (°C)	80	136	110	145

Styrofoam cups are derived from the aromatic compound styrene, PhCH═CH_2.

The common names **phenol**, **aniline**, **benzaldehyde**, **benzoic acid**, and **anisole** are also retained by the IUPAC system:



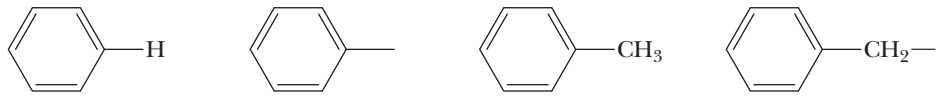
	Phenol	Aniline	Benzaldehyde	Benzoic acid	Anisole
mp (°C)	41	−6	−26	123	−37
bp (°C)	182	184	178	249	154

The physical properties of substituted benzenes vary depending on the nature of the substituent. Alkylbenzenes, like other hydrocarbons, are nonpolar and thus have lower boiling points than benzenes with polar substituents such as phenol, aniline, and benzoic acid. The melting points of substituted benzenes depend on whether or not their molecules can be packed close together. Benzene, which has no substituents and is flat, can pack its molecules very closely, giving it a considerably higher melting point than many substituted benzenes.

Phenyl group C_6H_5—, the aryl group derived by removing a hydrogen from benzene.

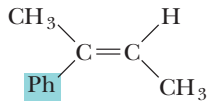
Benzyl group $C_6H_5CH_2$—, the alkyl group derived by removing a hydrogen from the methyl group of toluene.

The substituent group derived by the loss of an H from benzene is a **phenyl group** (Ph); that derived by the loss of an H from the methyl group of toluene is a **benzyl group** (Bn):



Benzene | Phenyl group (Ph) | Toluene | Benzyl group (Bn)

In molecules containing other functional groups, phenyl groups and benzyl groups are often named as substituents:



(*Z*)-2-Phenyl-2-butene

2-Phenylethanol

Benzyl chloride

B. Disubstituted Benzenes

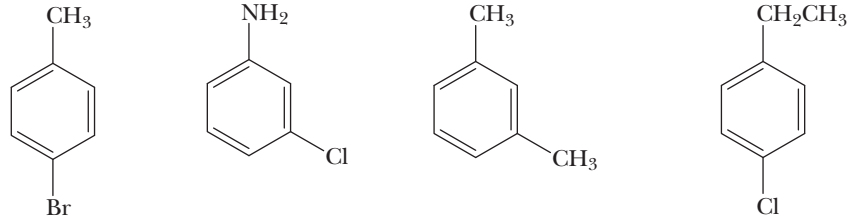
Ortho (*o*) Refers to groups occupying positions 1 and 2 on a benzene ring.

Meta (*m*) Refers to groups occupying positions 1 and 3 on a benzene ring.

Para (*p*) Refers to groups occupying positions 1 and 4 on a benzene ring.

When two substituents occur on a benzene ring, three constitutional isomers are possible. We locate substituents either by numbering the atoms of the ring or by using the locators **ortho**, **meta**, and **para**. The numbers 1,2- are equivalent to *ortho* (Greek: straight); 1,3- to *meta* (Greek: after); and 1,4- to *para* (Greek: beyond).

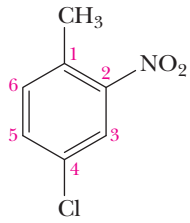
When one of the two substituents on the ring imparts a special name to the compound, as, for example, toluene, phenol, and aniline, then we name the compound as a derivative of that parent molecule. In this case, the special substituent occupies ring position number 1. The IUPAC system retains the common name **xylene** for the three isomeric dimethylbenzenes. When neither group imparts a special name, we locate the two substituents and list them in alphabetical order before the ending *-benzene*. The carbon of the benzene ring with the substituent of lower alphabetical ranking is numbered C-1.



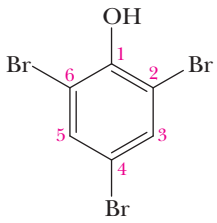
4-Bromotoluene (*p*-Bromotoluene) | 3-Chloroaniline (*m*-Chloroaniline) | 1,3-Dimethylbenzene (*m*-Xylene) | 1-Chloro-4-ethylbenzene (*p*-Chloroethylbenzene)

C. Polysubstituted Benzenes

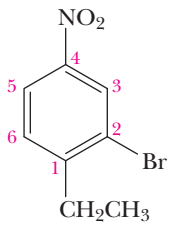
When three or more substituents are present on a ring, we specify their locations by numbers. If one of the substituents imparts a special name, then the molecule is named as a derivative of that parent molecule. If none of the substituents imparts a special name, we number them to give the smallest set of numbers and list them in alphabetical order before the ending *-benzene*. In the following examples, the first compound is a derivative of toluene, and the second is a derivative of phenol. Because there is no special name for the third compound, we list its three substituents in alphabetical order, followed by the word *benzene*:



4-Chloro-2-nitrotoluene



2,4,6-Tribromophenol



2-Bromo-1-ethyl-4-nitrobenzene

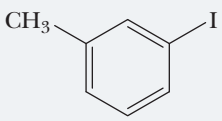
Charles D. Winters/Science Source Images

Moth balls are greater than 99% *para*-dichlorobenzene.

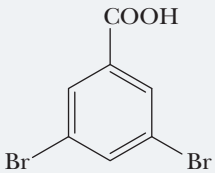
EXAMPLE 9.2

Write names for these compounds:

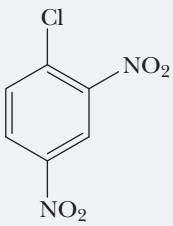
(a)



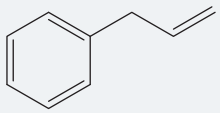
(b)



(c)



(d)



STRATEGY

First, determine whether one of the substituents imparts a special name to the benzene compound (e.g., toluene, phenol, aniline). Identify all substituents and list them in alphabetical order. Use numbers to indicate relative position. The locators *ortho*, *meta*, or *para* can be used for disubstituted benzenes.

SOLUTION

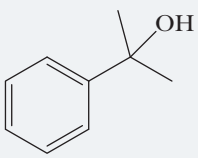
(a) 3-Iodotoluene or *m*-iodotoluene **(b)** 3,5-Dibromobenzoic acid **(c)** 1-Chloro-2,4-dinitrobenzene **(d)** 3-Phenylpropene

See problems 9.13, 9.14

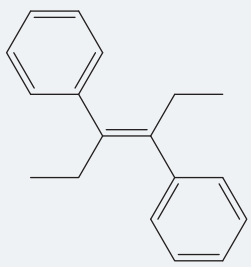
PROBLEM 9.2

Write names for these compounds:

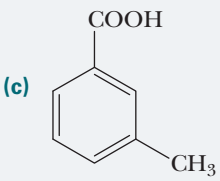
(a)



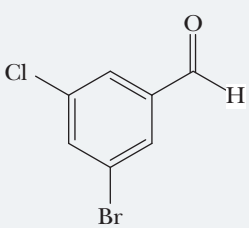
(b)



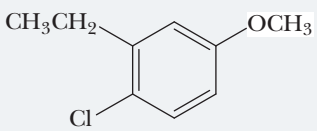
(c)



(d)

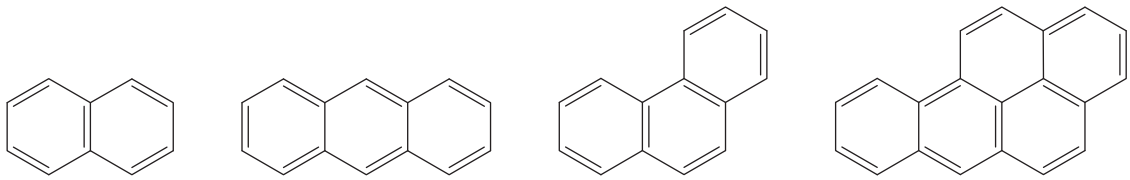


(e)



Polynuclear aromatic hydrocarbons A hydrocarbon containing two or more fused aromatic rings.

Polynuclear aromatic hydrocarbons (PAHs) contain two or more aromatic rings, each pair of which shares two ring carbon atoms. Naphthalene, anthracene, and phenanthrene, the most common PAHs, and substances derived from them are found in coal tar and high-boiling petroleum residues. At one time, naphthalene was used as a moth repellent and insecticide in protecting woolens and furs, but its use has decreased due to the introduction of chlorinated hydrocarbons such as *p*-dichlorobenzene. Also found in coal tar are lesser amounts of benzo[a]pyrene. This compound is found as well in the exhausts of gasoline-powered internal combustion engines (for example, automobile engines) and in cigarette smoke. Benzo[a]pyrene is a very potent carcinogen and mutagen (Chemical Connections 9A).



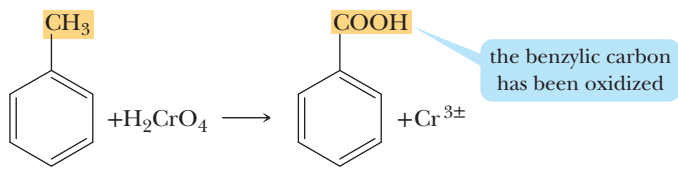
Naphthalene Anthracene Phenanthrene Benzo[a]pyrene

9.4 What Is a Benzylic Position, and How Does It Contribute to Benzene Reactivity?

As we have mentioned, benzene's aromaticity causes it to resist many of the reactions that alkenes typically undergo. However, chemists have been able to react benzene in other ways. This is fortunate because benzene rings are abundant in many of the compounds that society depends upon, including various medications, plastics, and preservatives for food. We begin our discussion of benzene reactions with processes that take place not on the ring itself, but at the carbon immediately bonded to the benzene ring. This carbon is known as a **benzylic carbon**.

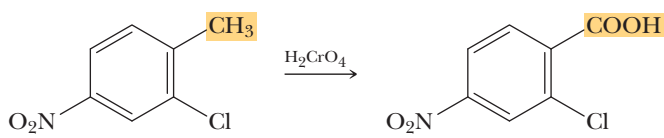
Benzylic carbon An sp^3 hybridized carbon bonded to a benzene ring.

Benzene is unaffected by strong oxidizing agents, such as H_2CrO_4 and $KMnO_4$. When we treat toluene with these oxidizing agents under vigorous conditions, the side-chain methyl group is oxidized to a carboxyl group to give benzoic acid:



Toluene Benzoic acid

The fact that the side-chain methyl group is oxidized, but the aromatic ring is unchanged, illustrates the remarkable chemical stability of an aromatic ring. Halogen and nitro substituents on an aromatic ring are unaffected by these oxidations. For example, chromic acid oxidizes 2-chloro-4-nitrotoluene to 2-chloro-4-nitrobenzoic acid. Notice that in this oxidation, the nitro and chloro groups remain unaffected:



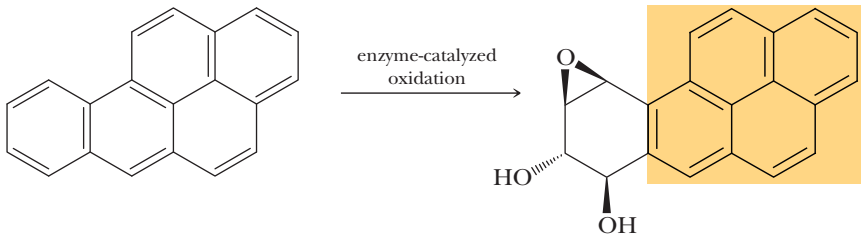
2-Chloro-4-nitrotoluene 2-Chloro-4-nitrobenzoic acid

Chemical Connections 9A

CARCINOGENIC POLYNUCLEAR AROMATICS AND CANCER

A **carcinogen** is a compound that causes cancer. The first carcinogens to be identified were a group of polynuclear aromatic hydrocarbons, all of which have at least four aromatic rings. Among them is benzo[a]pyrene, one of the most carcinogenic of the aromatic hydrocarbons. It forms whenever there is incomplete combustion of organic compounds. Benzo[a]pyrene is found, for example, in cigarette smoke, automobile exhaust, and charcoal-broiled meats.

Benzo[a]pyrene causes cancer in the following way: Once it is absorbed or ingested, the body attempts to convert it into a more soluble compound that can be excreted easily. To this end, a series of enzyme-catalyzed reactions transforms benzo[a]pyrene into a **diol epoxide**, a compound that can bind to DNA by reacting with one of its amino groups, thereby altering the structure of DNA and producing a cancer-causing mutation:

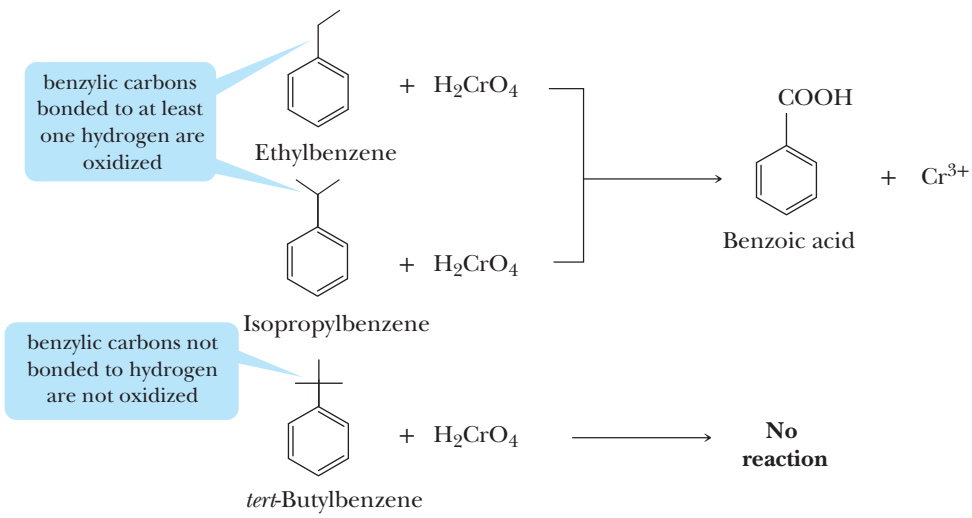


Benzo[a]pyrene — A diol epoxide

Question

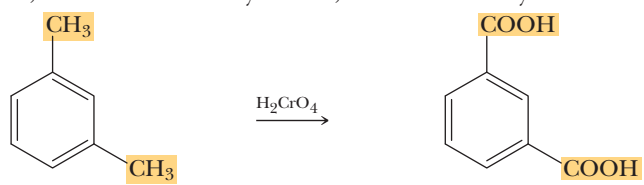
Show how the outer perimeter of benzo[a]pyrene satisfies Hückel's criteria for aromaticity. Is the outer perimeter of the highlighted portion of the diol epoxide product of benzo[a]pyrene also aromatic?

Ethylbenzene and isopropylbenzene are also oxidized to benzoic acid under these conditions. The side chain of *tert*-butylbenzene, which has no benzylic hydrogen, is not affected by these oxidizing conditions.



From these observations, we conclude that, if a benzylic hydrogen exists, then the benzylic carbon (Section 9.3A) is oxidized to a carboxyl group and all other carbons of the side chain are removed. If no benzylic hydrogen exists, as in the case of *tert*-butylbenzene, then the side chain is not oxidized.

If more than one alkyl side chain exists, each is oxidized to —COOH. Oxidation of *m*-xylene gives 1,3-benzenedicarboxylic acid, more commonly named isophthalic acid:

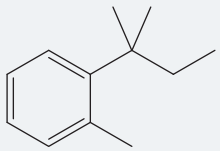


m-Xylene — 1,3-Benzenedicarboxylic acid (Isophthalic acid)

EXAMPLE 9.3

Predict the products resulting from vigorous oxidation of each compound by H_2CrO_4. The various by-products that are formed from benzylic oxidation reactions are usually not specified.

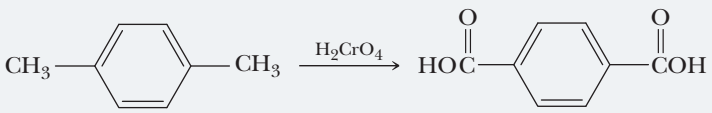
(a) 1,4-dimethylbenzene (*p*-xylene)

(b) 

STRATEGY

Identify all the alkyl groups in the reactant. If a benzylic hydrogen exists on an alkyl group, chromic acid will oxidize it to a —COOH group.

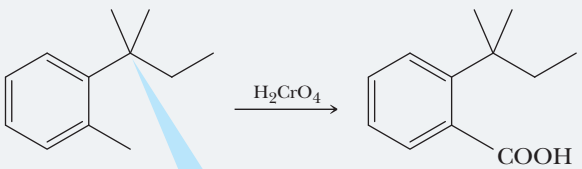
SOLUTION

(a) 

1,4-Dimethylbenzene (*p*-Xylene)

1,4-Benzenedicarboxylic acid (Terephthalic acid)

chromic acid oxidizes both alkyl groups to —COOH groups, and the product is terephthalic acid, one of two compounds required for the synthesis of Dacron polyester and Mylar (Section 17.4B)

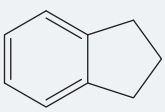
(b) 

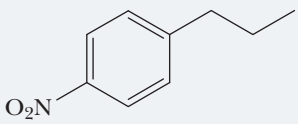
this alkyl group has no benzylic hydrogens and is not oxidized

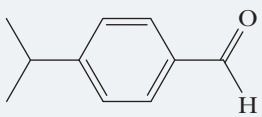
See problem 9.30

PROBLEM 9.3

Predict the products resulting from vigorous oxidation of each compound by H_2CrO_4:

(a) 

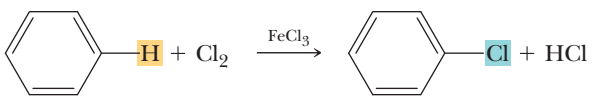
(b) 

(c) 

9.5 What Is Electrophilic Aromatic Substitution?

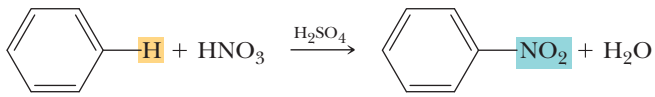
Although benzene is resistant to most of the reactions presented thus far for alkenes, it is not completely unreactive. By far the most characteristic reaction of aromatic compounds is substitution at a ring carbon. Some groups that can be introduced directly onto the ring are the halogens, the nitro (—NO_2) group, the sulfonic acid (—SO_3H) group, alkyl (—R) groups, and acyl (RCO—) groups.

Halogenation:



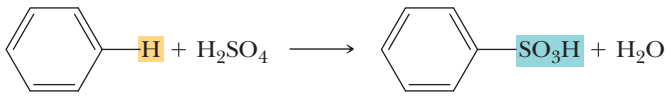
Chlorobenzene

Nitration:



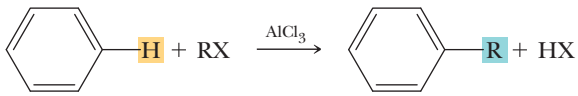
Nitrobenzene

Sulfonation:



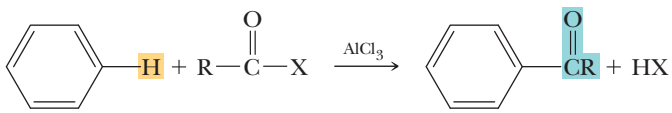
Benzenesulfonic acid

Alkylation:



An alkylbenzene

Acylation:



An acyl halide

An acylbenzene

9.6 What Is the Mechanism of Electrophilic Aromatic Substitution?

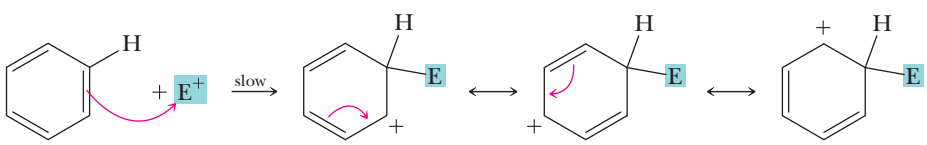
In this section, we study several types of **electrophilic aromatic substitution** reactions—that is, reactions in which a hydrogen of an aromatic ring is replaced by an electrophile, E^+. The mechanisms of these reactions are actually very similar. In fact, they can be broken down into three common steps:

Electrophilic aromatic substitution A reaction in which an electrophile, E^+, substitutes for a hydrogen on an aromatic ring.

Step 1: **Generation of the electrophile.** This is a reaction pattern specific to each particular electrophilic aromatic substitution reaction.

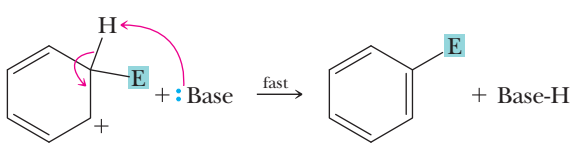
$$\text{Reagent(s)} \rightarrow E^+$$

Step 2: **Reaction of a nucleophile and an electrophile to form a new covalent bond.** Attack of the electrophile on the aromatic ring to give a resonance-stabilized cation intermediate:



(the nucleophile) Resonance-stabilized cation intermediate

Step 3: **Take a proton away.** Proton transfer to a base to regenerate the aromatic ring:



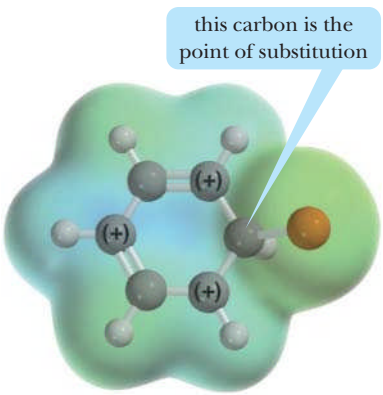
The reactions we are about to study differ only in the way the electrophile is generated and in the base that removes the proton to re-form the aromatic ring. You should keep this principle in mind as we explore the details of each reaction.

A. Chlorination and Bromination

Chlorine alone does not react with benzene, in contrast to its instantaneous addition to cyclohexene (Section 5.3C). However, in the presence of a Lewis acid catalyst, such as ferric chloride or aluminum chloride, chlorine reacts to give chlorobenzene and HCl. Chemists account for this type of electrophilic aromatic substitution by the following three-step mechanism:

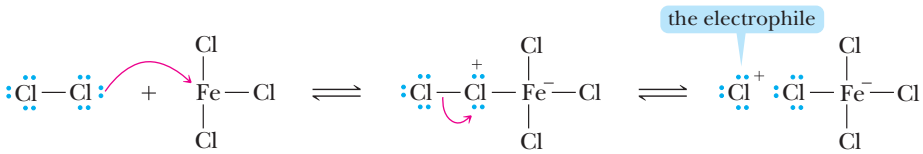
Mechanism

Electrophilic Aromatic Substitution—Chlorination



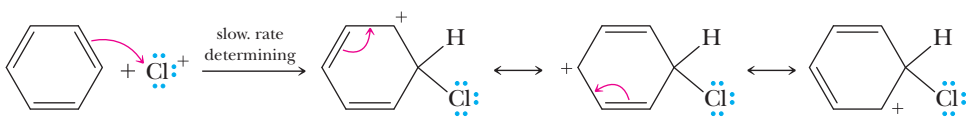
The positive charge on the resonance-stabilized intermediate is distributed approximately equally on the carbon atoms 2, 4, and 6 of the ring relative to the point of substitution.

STEP 1: *Formation of the Electrophile.*
Reaction between chlorine (a Lewis base) and $FeCl_3$ (a Lewis acid) gives an ion pair containing a chloronium ion (an electrophile):



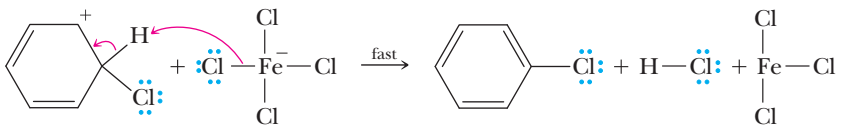
Chlorine (a Lewis base) | Ferric chloride (a Lewis acid) | A molecular complex with a positive charge on chlorine and a negative charge on iron | An ion pair containing a chloronium ion

STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction of the Cl_2–$FeCl_3$ ion pair with the pi electron cloud of the aromatic ring forms a resonance-stabilized cation intermediate, represented here as a hybrid of three contributing structures:



(the nucleophile) | Resonance-stabilized cation intermediate

STEP 3: *Take a proton away.*
Proton transfer from the cation intermediate to $FeCl_4^-$ forms HCl, regenerates the Lewis acid catalyst, and gives chlorobenzene:



Cation intermediate | Chlorobenzene

Treatment of benzene with bromine in the presence of ferric chloride or aluminum chloride gives bromobenzene and HBr. The mechanism for this reaction is the same as that for chlorination of benzene.

The major difference between the addition of halogen to an alkene and substitution by halogen on an aromatic ring is the fate of the cation intermediate formed after the

halogen is added to the compound. Recall from Section 5.3C that the addition of chlorine to an alkene is a two-step process, the first and slower step of which is the formation of a bridged chloronium ion intermediate. This intermediate then reacts with chloride ion to complete the addition. With aromatic compounds, the cation intermediate loses H^+ to regenerate the aromatic ring and the enhanced stability this provides. There is no such aromaticity to be regained in the case of an alkene.

B. Nitration and Sulfonation

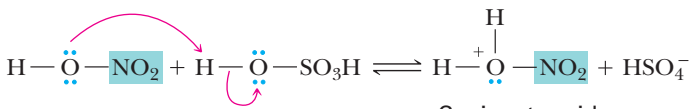
The sequence of steps for the nitration and sulfonation of benzene is similar to that for chlorination and bromination. For nitration, the electrophile is the **nitronium ion**, NO_2^+, generated by the reaction of nitric acid with sulfuric acid. In the following equations nitric acid is written $HONO_2$ to show more clearly the origin of the nitronium ion.

Mechanism

Formation of the Nitronium Ion

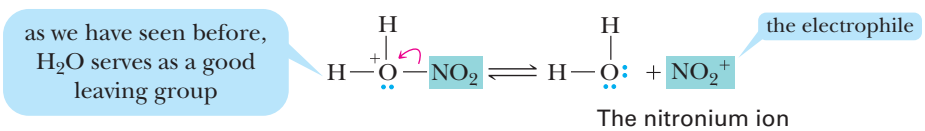
STEP 1: *Add a proton.*

Proton transfer from sulfuric acid to the OH group of nitric acid gives the conjugate acid of nitric acid:



STEP 2: *Break a bond to form a stable ion or molecule.*

Loss of water from this conjugate acid gives the nitronium ion, NO_2^+:



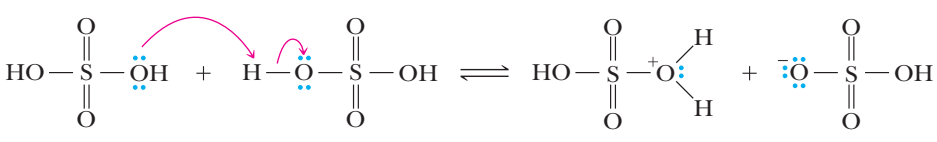
Mechanism

Formation of the Sulfonium Ion

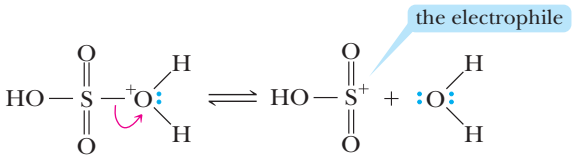
The sulfonation of benzene is carried out using hot, concentrated sulfuric acid. The electrophile under these conditions is either SO_3 or HSO_3^+, depending on the experimental conditions. The HSO_3^+ electrophile is formed from sulfuric acid in the following way:

STEP 1: *Add a proton.*

Proton transfer from one molecule of sulfuric acid to the OH group of another molecule of sulfuric acid gives the conjugate acid of sulfuric acid:



STEP 2: *Break a bond to form a more stable ion or molecule.*
Loss of water from this conjugate acid gives the sulfonium ion as the electrophile:



The sulfonium ion

EXAMPLE 9.4

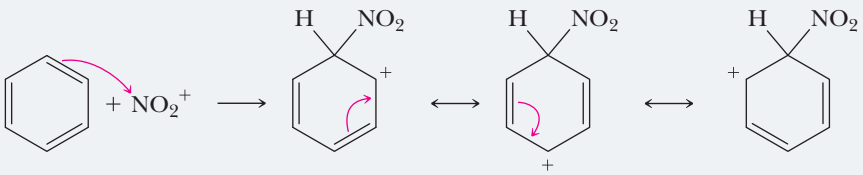
Write a stepwise mechanism for the nitration of benzene.

STRATEGY

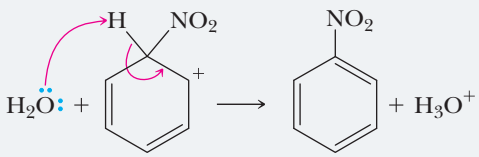
Keep in mind that the mechanisms of electrophilic aromatic substitution reactions are all very similar. After the formation of the electrophile, attack of the electrophile on the aromatic ring occurs to give a resonance-stabilized cation intermediate. The last step of the mechanism is proton transfer to a base to regenerate the aromatic ring. The base in nitration is water, which was generated in the formation of the electrophile.

SOLUTION

STEP 1: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction of the nitronium ion (an electrophile) with the benzene ring (a nucleophile) gives a resonance-stabilized cation intermediate.



STEP 2: *Take a proton away.*
Proton transfer from this intermediate to H_2O regenerates the aromatic ring and gives nitrobenzene:



Nitrobenzene

See problems 9.21, 9.22

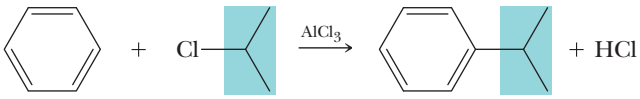
PROBLEM 9.4

Write a stepwise mechanism for the sulfonation of benzene. Use HSO_3^+ as the electrophile.

C. Friedel–Crafts Alkylation

Alkylation of aromatic hydrocarbons was discovered in 1877 by the French chemist Charles Friedel and a visiting American chemist, James Crafts. They discovered that mixing benzene, a haloalkane, and $AlCl_3$ results in the formation of an alkylbenzene and HX.

Friedel–Crafts alkylation forms a new carbon–carbon bond between benzene and an alkyl group, as illustrated by reaction of benzene with 2-chloropropane in the presence of aluminum chloride:



Benzene — 2-Chloropropane (Isopropyl chloride) — Isopropylbenzene (Cumene)

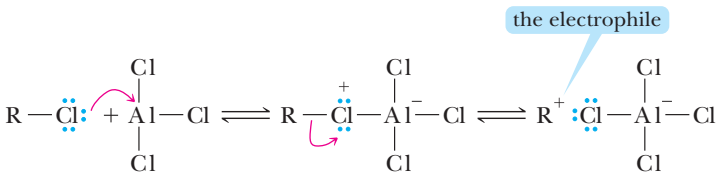
Friedel–Crafts alkylation is among the most important methods for forming new carbon–carbon bonds to aromatic rings.

Mechanism

Friedel–Crafts Alkylation

STEP 1: *Formation of an electrophile.*

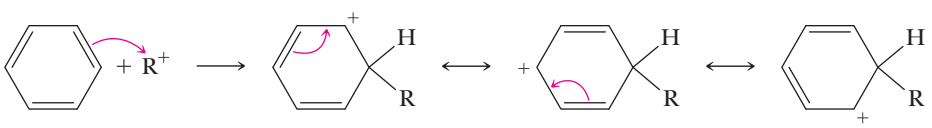
Reaction of a haloalkane (a Lewis base) with aluminum chloride (a Lewis acid) gives a molecular complex in which aluminum has a negative formal charge and the halogen of the haloalkane has a positive formal charge. Redistribution of electrons in this complex then gives an alkyl carbocation as part of an ion pair:



A molecular complex with a positive charge on chlorine and a negative charge on aluminum — An ion pair containing a carbocation

STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*

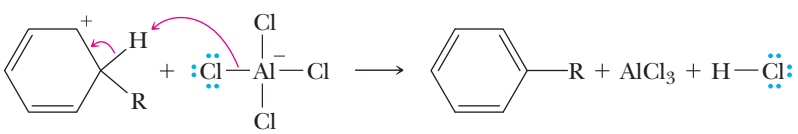
Reaction of the alkyl carbocation with the pi electrons of the aromatic ring gives a resonance-stabilized cation intermediate:



The positive charge is delocalized onto three atoms of the ring

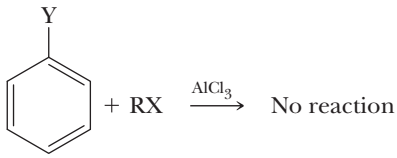
STEP 3: *Take a proton away.*

Proton transfer regenerates the aromatic character of the ring and the Lewis acid catalyst:



There are two major limitations on Friedel–Crafts alkylations. The first is that it is practical only with stable carbocations, such as 3° carbocations, resonance-stabilized carbocations, or 2° carbocations that cannot undergo rearrangement (Section 5.4). Primary carbocations will undergo rearrangement, resulting in multiple products as well as bonding of the benzene ring to unexpected carbons in the former haloalkane.

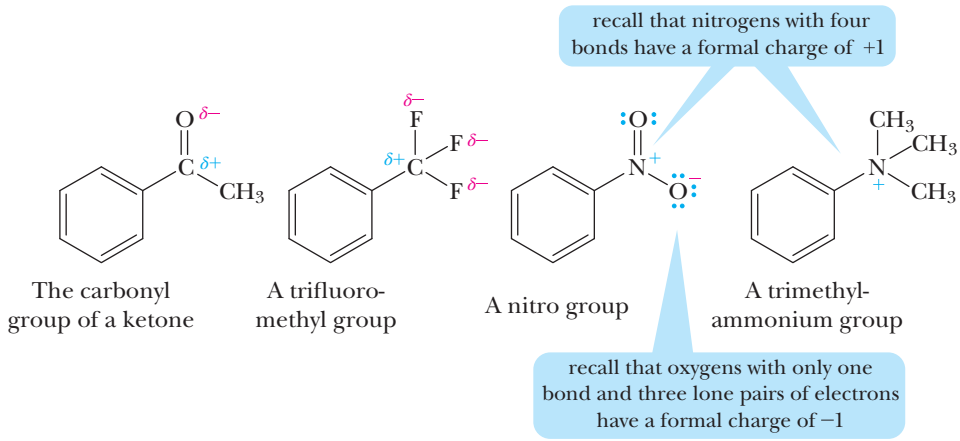
The second limitation on Friedel–Crafts alkylation is that it fails altogether on benzene rings bearing one or more strongly electron-withdrawing groups. The following table shows some of these groups:



When Y Equals Any of These Groups, the Benzene Ring Does Not Undergo Friedel–Crafts Alkylation

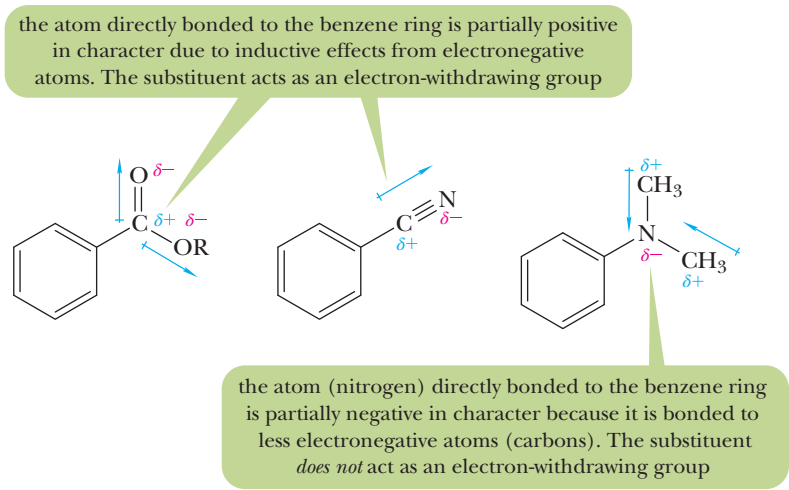
—CHO	—COR	—COOH	—COR	—CNH_2
—SO_3H	—C≡N	—NO_2	—NR_3^+	
—CF_3	—CCl_3			

A common characteristic of the groups listed in the preceding table is that each has either a full or partial positive charge on the atom bonded to the benzene ring. For carbonyl-containing compounds, this partial positive charge arises because of the difference in electronegativity between the carbonyl oxygen and carbon. For —CF_3 and —CCl_3 groups, the partial positive charge on carbon arises because of the difference in electronegativity between carbon and the halogens bonded to it. In both the nitro group and the trialkylammonium group, there is a positive charge on nitrogen:



HOW TO 9.2 Determine Whether a Substituent on Benzene Is Electron Withdrawing

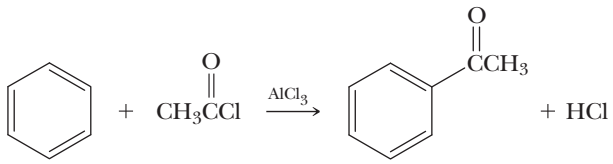
Determine the charge or partial charge on the atom directly bonded to the benzene ring. If it is positive or partially positive, the substituent can be considered to be electron withdrawing. An atom will be partially positive if it is bonded to an atom more electronegative than itself.



D. Friedel–Crafts Acylation

Friedel and Crafts also discovered that treating an aromatic hydrocarbon with an acyl halide in the presence of aluminum chloride gives a ketone. An **acyl halide** is a derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen, most commonly chlorine. Acyl halides are also referred to as acid halides. An RCO— group is known as an acyl group; hence, the reaction of an acyl halide with an aromatic hydrocarbon is known as **Friedel–Crafts acylation**, as illustrated by the reaction of benzene and acetyl chloride in the presence of aluminum chloride to give acetophenone:

Acyl halide A derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen—most commonly, chlorine.



Benzene | Acetyl chloride (an acyl halide) | Acetophenone (a ketone)

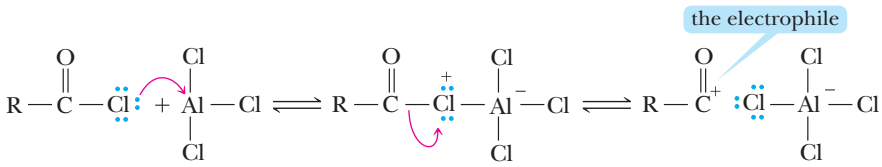
In Friedel–Crafts acylations, the electrophile is an acylium ion, generated in the following way:

Mechanism

Friedel–Crafts Acylation—Generation of an Acylium Ion

STEP 1: *Formation of an electrophile.*

Reaction between the halogen atom of the acyl chloride (a Lewis base) and aluminum chloride (a Lewis acid) gives a molecular complex. The redistribution of valence electrons in turn gives an ion pair containing an **acylium ion**:

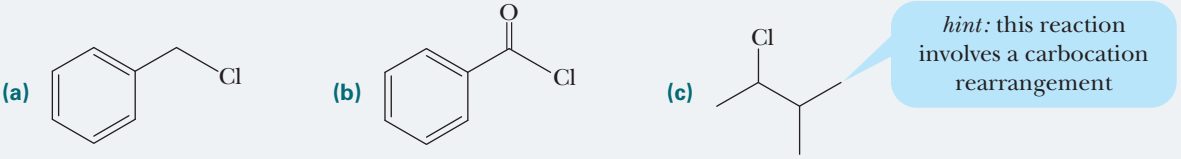


An acyl chloride (a Lewis acid) | Aluminum chloride (a Lewis acid) | A molecular complex with a positive charge on chlorine and a negative charge on aluminum | An ion pair containing an acylium ion

Steps 2 and 3 are identical to steps 2 and 3 of Friedel–Crafts alkylation (Section 9.6C).

EXAMPLE 9.5

Write a structural formula for the product formed by Friedel–Crafts alkylation or acylation of benzene with

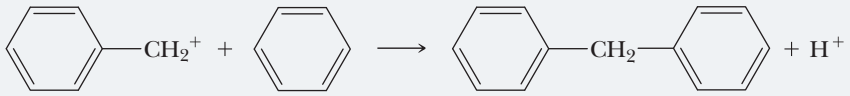


STRATEGY

Utilize the fact that the halogenated reagent in Friedel–Crafts reactions will normally form a bond with benzene at the carbon bonded to the halogen (Br or Cl). Therefore, to predict the product of a Friedel–Crafts reaction, replace the halogen in the haloalkane or acyl halide with the benzene ring. One thing to be wary of, however, is the possibility of rearrangement once the carbocation is formed.

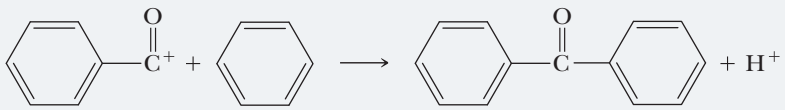
SOLUTION

(a) Treatment of benzyl chloride with aluminum chloride gives the resonance-stabilized benzyl cation. Reaction of this cation (an electrophile) with benzene (a nucleophile), followed by loss of H^+, gives diphenylmethane:



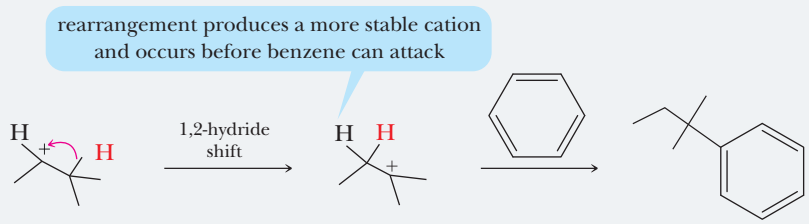
Benzyl cation (an electrophile) (a nucleophile) Diphenylmethane

(b) Treatment of benzoyl chloride with aluminum chloride gives an acyl cation. Reaction of this cation with benzene, followed by loss of H^+, gives benzophenone:



Benzoyl cation (an electrophile) Benzophenone

(c) Treatment of 2-chloro-3-methylbutane with aluminum chloride gives a 2° carbocation. Because there is an adjacent 3° hydrogen, a 1,2-hydride shift can occur to form the more stable 3° carbocation. It is this carbon that reacts with benzene, followed by loss of H^+, to give 2-methyl-2-phenylbutane.

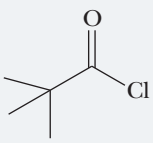


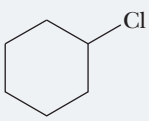
A 2° carbocation A 3° carbocation 2-Methyl-2-phenylbutane

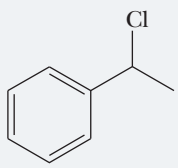
See problems 9.18, 9.19

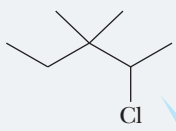
PROBLEM 9.5

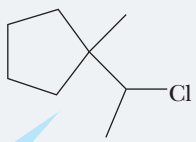
Write a structural formula for the product formed from Friedel–Crafts alkylation or acylation of benzene with

(a) 

(b) 

(c) 

(d) 

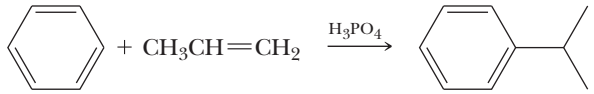
(e) 

hint: these two involve a carbocation rearrangement

E. Other Electrophilic Aromatic Alkylations

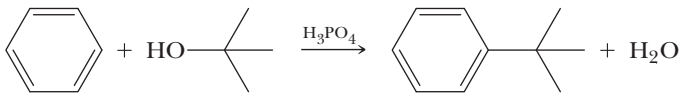
Once it was discovered that Friedel–Crafts alkylations and acylations involve cationic intermediates, chemists realized that other combinations of reagents and catalysts could give the same intermediates. We study two of these reactions in this section: the generation of carbocations from alkenes and from alcohols.

As we saw in Section 5.3B, treatment of an alkene with a strong acid, most commonly H_2SO_4 or H_3PO_4, generates a carbocation. Isopropylbenzene is synthesized industrially by reacting benzene with propene in the presence of an acid catalyst:



Benzene Propene Isopropylbenzene (Cumene)

Carbocations are also generated by treating an alcohol with H_2SO_4 or H_3PO_4 (Section 8.2E):



Benzene 2-Methyl-2-phenylpropane (*tert*-Butylbenzene)

EXAMPLE 9.6

Write a mechanism for the formation of isopropylbenzene from benzene and propene in the presence of phosphoric acid.

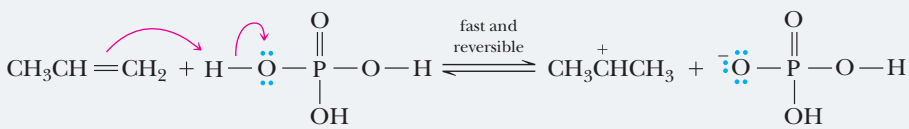
STRATEGY

Draw the mechanism for the formation of the carbocation. This step constitutes the generation of the electrophile. The remaining steps in the mechanism are the usual: attack of the electrophile on benzene and proton transfer to rearomatize the ring.

SOLUTION

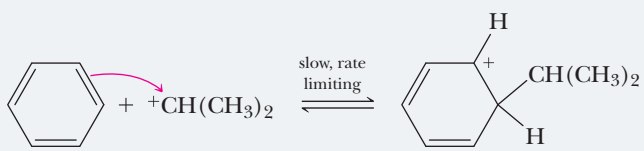
STEP 1: *Add a proton.*

Proton transfer from phosphoric acid to propene gives the isopropyl cation:



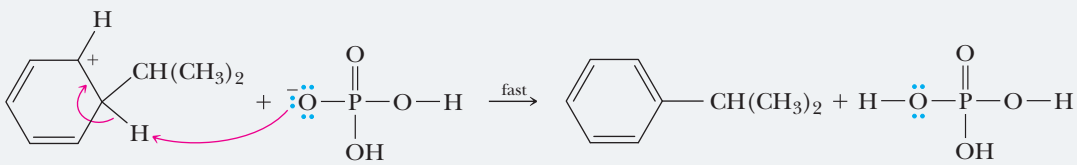
STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*

Reaction of the isopropyl cation with benzene gives a resonance-stabilized carbocation intermediate:



STEP 3: *Take a proton away.*

Proton transfer from this intermediate to dihydrogen phosphate ion gives isopropylbenzene:



Isopropylbenzene

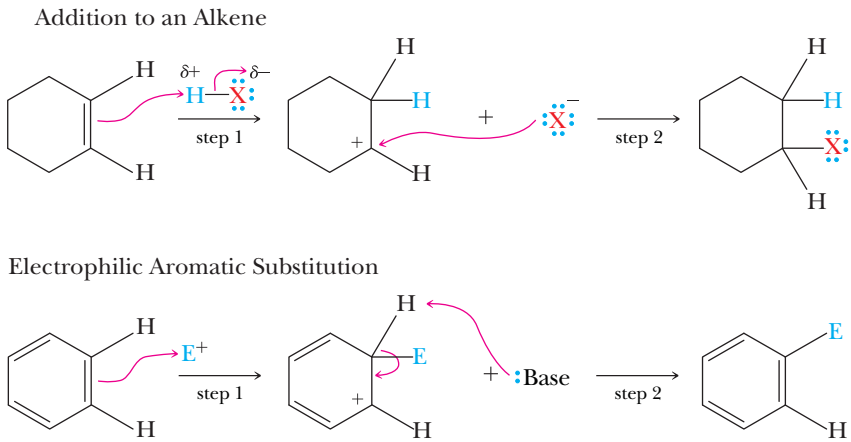
See problems 9.18, 9.19, 9.33, 9.34

PROBLEM 9.6

Write a mechanism for the formation of *tert*-butylbenzene from benzene and *tert*-butyl alcohol in the presence of phosphoric acid.

F. Comparison of Alkene Addition and Electrophilic Aromatic Substitution (EAS)

Electrophilic aromatic substitution represents the second instance in which we have encountered a C═C double bond attacking an electrophile. The first instance was in our discussion of alkene addition reactions in Section 5.3. Notice the similarities in the first step where a C═C double bond attacks an electrophilic atom (H^+ or E^+). In Step 2, however, alkene addition results in the attack of a nucleophile on the carbocation, while EAS results in abstraction of a hydrogen by base. In one reaction, the C═C double bond is destroyed, while in the other, the C═C double bond is regenerated.



9.7 How Do Existing Substituents on Benzene Affect Electrophilic Aromatic Substitution?

A. Effects of a Substituent Group on Further Substitution

Ortho–para directing Any substituent on a benzene ring that directs electrophilic aromatic substitution preferentially to ortho and para positions.

Meta directing Any substituent on a benzene ring that directs electrophilic aromatic substitution preferentially to a meta position.

Activating group Any substituent on a benzene ring that causes the rate of electrophilic aromatic substitution to be greater than that for benzene.

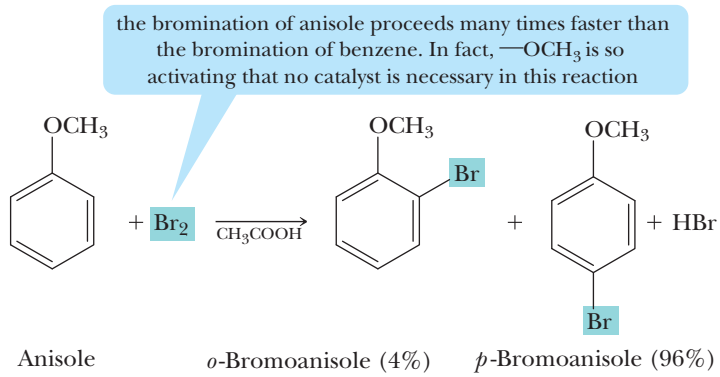
Deactivating group Any substituent on a benzene ring that causes the rate of electrophilic aromatic substitution to be lower than that for benzene.

In the electrophilic aromatic substitution of a monosubstituted benzene, three isomeric products are possible: The new group may be oriented ortho, meta, or para to the existing group. On the basis of a wealth of experimental observations, chemists have made the following generalizations about the manner in which an existing substituent influences further electrophilic aromatic substitution:

1. *Substituents affect the orientation of new groups.* Certain substituents direct a second substituent preferentially to the ortho and para positions; other substituents direct it preferentially to a meta position. In other words, we can classify substituents on a benzene ring as **ortho–para directing** or **meta directing**.

2. *Substituents affect the rate of further substitution.* Certain substituents cause the rate of a second substitution to be greater than that of benzene itself, whereas other substituents cause the rate of a second substitution to be lower than that of benzene. In other words, we can classify groups on a benzene ring as **activating** or **deactivating** toward further substitution.

To see the operation of these directing and activating–deactivating effects, compare, for example, the products and rates of bromination of anisole and nitrobenzene. Bromination of anisole proceeds at a rate 1.8×10^9 greater than that of bromination of benzene (the methoxy group is activating), and the product is a mixture of *o*-bromoanisole and *p*-bromoanisole (the methoxy group is ortho–para directing):



We see quite another situation in the nitration of nitrobenzene, which proceeds 10,000 times slower than the nitration of benzene itself. (A nitro group is strongly deactivating.) Also, the product consists of approximately 93% of the meta isomer and less than 7% of the ortho and para isomers combined (the nitro group is meta directing):

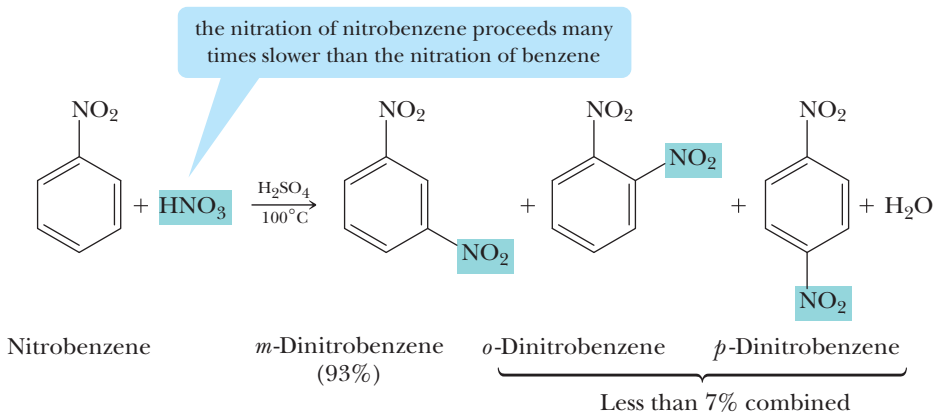
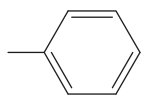


Table 9.1 lists the directing and activating–deactivating effects for the major functional groups with which we are concerned in this text.

TABLE 9.1 Effects of Substituents on Further Electrophilic Aromatic Substitution

Ortho–Para Directing	strongly activating	—$\ddot{N}H_2$	—$\ddot{N}HR$	—$\ddot{N}R_2$	—$\ddot{O}H$	—$\ddot{O}R$		
	moderately activating	—$\ddot{N}HCR$ (O)	—$\ddot{N}HCAr$ (O)	—$\ddot{O}CR$ (O)	—$\ddot{O}CAr$ (O)			
	weakly activating	—R						
	weakly deactivating	—$\ddot{F}$:	—$\ddot{C}l$:	—$\ddot{B}r$:	—$\ddot{I}$:			
Meta Directing	moderately deactivating	—CH (O)	—CR (O)	—COH (O)	—COR (O)	—CNH_2 (O)	—SOH (O, O)	
	strongly deactivating	—NO_2	—NH_3^+	—CF_3	—CCl_3			

Relative importance in directing further substitution

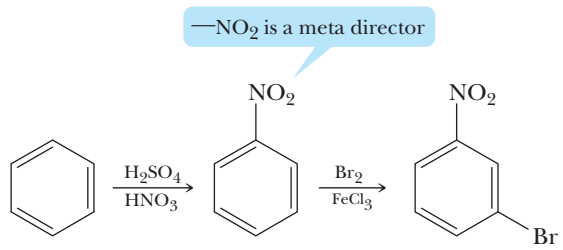
increasing reactivity relative to benzene

decreasing reactivity relative to benzene

If we compare these ortho–para and meta directors for structural similarities and differences, we can make the following generalizations:

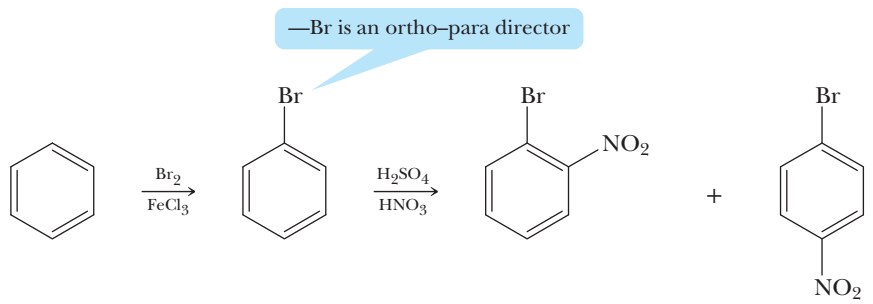
1. Alkyl groups, phenyl groups, and substituents in which the atom bonded to the ring has an unshared pair of electrons are ortho–para directing. All other substituents are meta directing.
2. Except for the halogens, all ortho–para directing groups are activating toward further substitution. The halogens are weakly deactivating.
3. All meta directing groups carry either a partial or full positive charge on the atom bonded to the ring. All meta directing groups are deactivating.

We can illustrate the usefulness of these generalizations by considering the synthesis of two different disubstituted derivatives of benzene. Suppose we wish to prepare *m*-bromonitrobenzene from benzene. This conversion can be carried out in two steps: nitration and bromination. If the steps are carried out in just that order, the major product is indeed *m*-bromonitrobenzene. The nitro group is a meta director and directs bromination to a meta position:



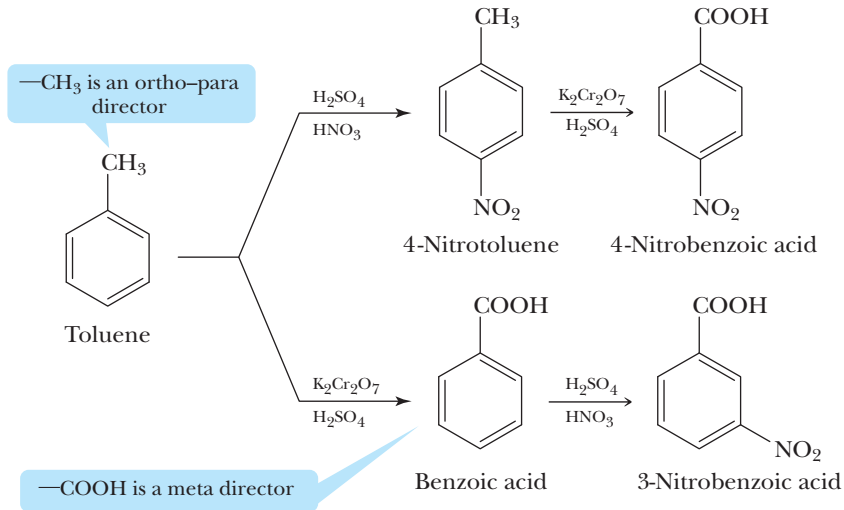
Nitrobenzene *m*-Bromonitrobenzene

If, however, we reverse the order of the steps and first form bromobenzene, we now have an ortho–para directing group on the ring. Nitration of bromobenzene then takes place preferentially at the ortho and para positions, with the para product predominating:



Bromobenzene *o*-Bromonitrobenzene *p*-Bromonitrobenzene

As another example of the importance of order in electrophilic aromatic substitutions, consider the conversion of toluene to nitrobenzoic acid. The nitro group can be introduced with a nitrating mixture of nitric and sulfuric acids. The carboxyl group can be produced by oxidation of the methyl group (Section 9.4).

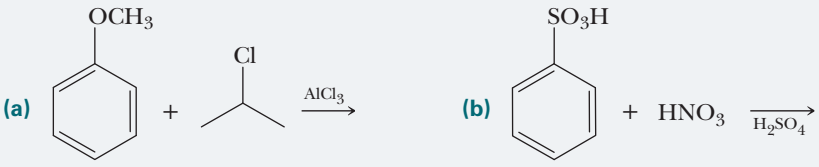


Nitration of toluene yields a product with the two substituents para to each other, whereas nitration of benzoic acid yields a product with the substituents meta to each other. Again, we see that the order in which the reactions are performed is critical.

Note that, in this last example, we show nitration of toluene producing only the para isomer. In practice, because methyl is an ortho–para directing group, both ortho and para isomers are formed. In problems in which we ask you to prepare one or the other of these isomers, we assume that both form and that there are physical methods by which you can separate them and obtain the desired isomer.

EXAMPLE 9.7

Complete the following electrophilic aromatic substitution reactions. Where you predict meta substitution, show only the meta product. Where you predict ortho–para substitution, show both ortho and para products:

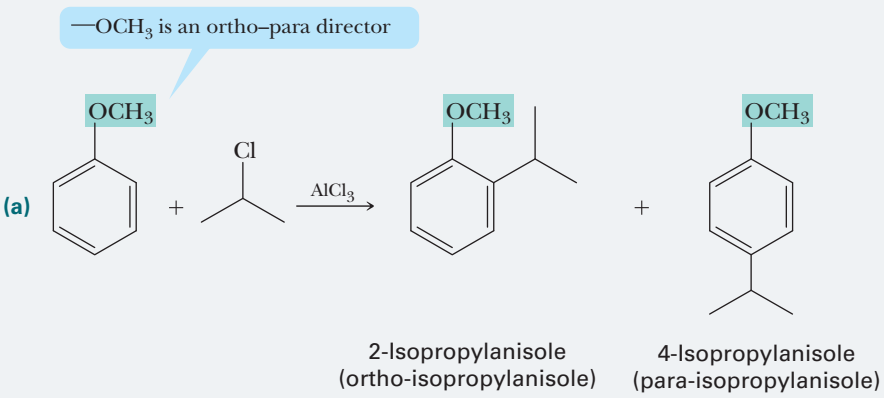


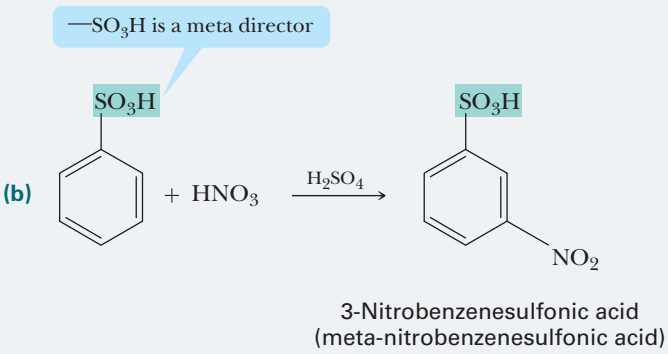
STRATEGY

Determine whether the existing substituent is ortho–para or meta directing prior to completing the reaction.

SOLUTION

The methoxyl group in (a) is ortho–para directing and strongly activating. The sulfonic acid group in (b) is meta directing and moderately deactivating.

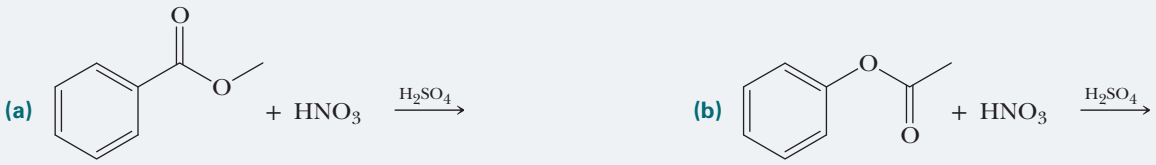




See problems 9.24–9.26, 9.31, 9.32, 9.42–9.44, 9.46, 9.47

PROBLEM 9.7

Complete the following electrophilic aromatic substitution reactions. Where you predict meta substitution, show only the meta product. Where you predict ortho–para substitution, show both ortho and para products:



B. Theory of Directing Effects

As we have just seen, a group on an aromatic ring exerts a major effect on the patterns of further substitution. We account for these patterns by means of the general mechanism for electrophilic aromatic substitution first presented in Section 9.5. Let us extend that mechanism to consider how a group already present on the ring might affect the relative stabilities of cation intermediates formed during a second substitution reaction.

We begin with the fact that the rate of electrophilic aromatic substitution is determined by the slowest step in the mechanism, which, in almost every reaction of an electrophile with the aromatic ring, is attack of the electrophile on the ring to give a resonance-stabilized cation intermediate. Thus, we must determine which of the alternative carbocation intermediates (that for ortho–para substitution or that for meta substitution) is the more stable. That is, we need to show which of the alternative cationic intermediates has the lower activation energy for its formation.

Nitration of Anisole

The rate-determining step in nitration is reaction of the nitronium ion with the aromatic ring to produce a resonance-stabilized cation intermediate. Figure 9.4 shows the cation intermediate formed by reaction meta to the methoxy group. The figure also shows the cationic intermediate formed by reaction para to the methoxy group. The intermediate formed by reaction at a meta position is a hybrid of three major contributing structures: (a), (b), and (c). These three are the only important contributing structures we can draw for reaction at a meta position.

The cationic intermediate formed by reaction at the para position is a hybrid of four major contributing structures: (d), (e), (f), and (g). What is important about structure (f) is that all

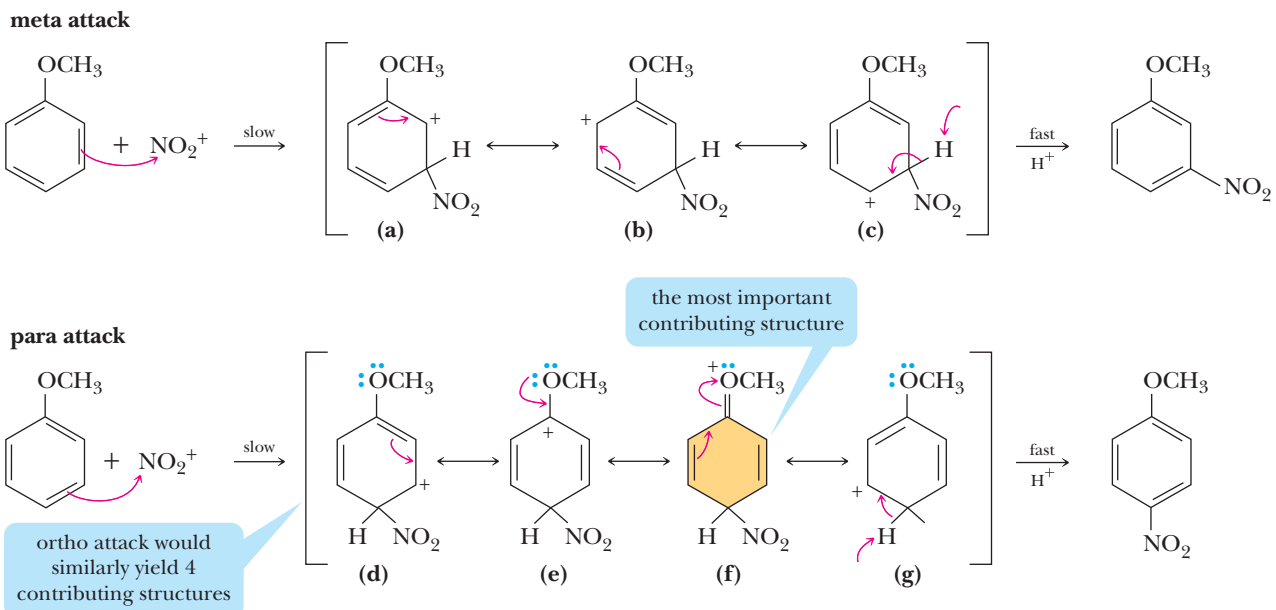


FIGURE 9.4 Nitration of anisole. Reaction of the electrophile meta and para to a methoxy group. Regeneration of the aromatic ring is shown from the rightmost contributing structure in each case.

atoms in it have complete octets, which means that this structure contributes more to the hybrid than structures (d), (e), or (g). Because the cation formed by reaction at an ortho or para position on anisole has a greater resonance stabilization and, hence, a lower activation energy for its formation, nitration of anisole occurs preferentially in the ortho and para positions.

Nitration of Nitrobenzene

Figure 9.5 shows the resonance-stabilized cation intermediates formed by reaction of the nitronium ion meta to the nitro group and also para to it.

Each cation in the figure is a hybrid of three contributing structures; no additional ones can be drawn. Now we must compare the relative resonance stabilizations of each

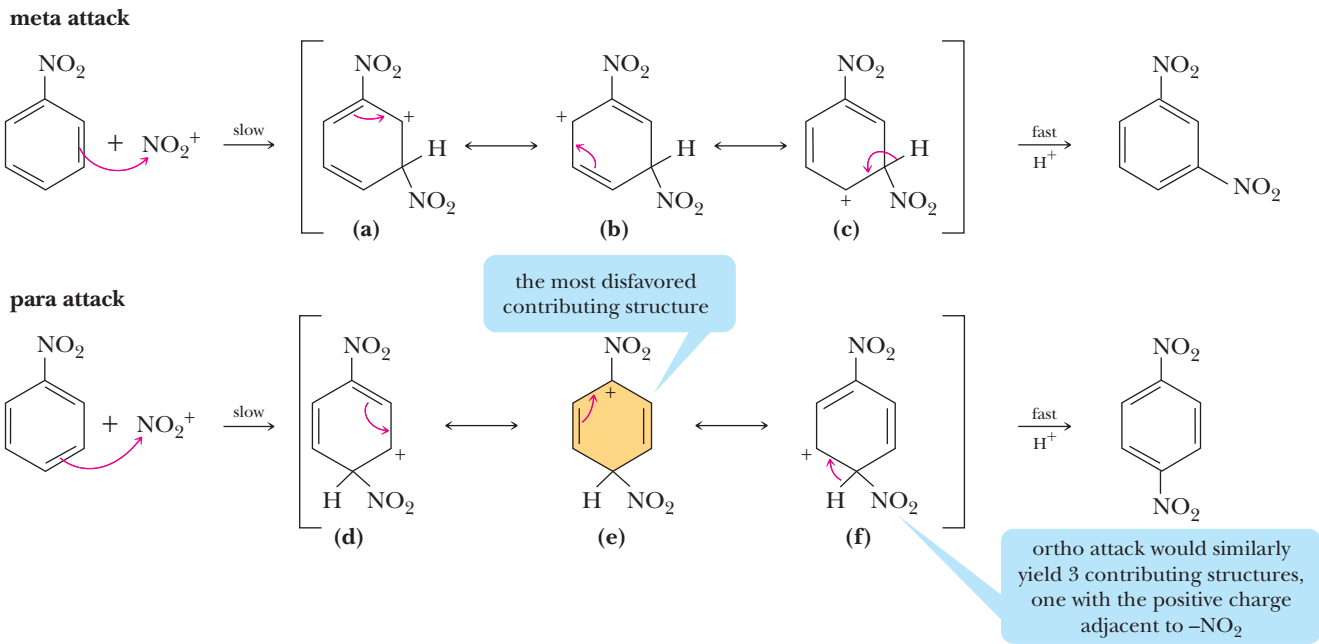
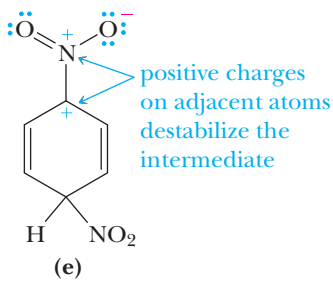


FIGURE 9.5 Nitration of nitrobenzene. Reaction of the electrophile meta and para to a nitro group. Regeneration of the aromatic ring is shown from the rightmost contributing structure in each case.

hybrid. If we draw a Lewis structure for the nitro group showing the positive formal charge on nitrogen, we see that contributing structure (e) places positive charges on adjacent atoms:



Because of the electrostatic repulsion thus generated, structure (e) makes only a negligible contribution to the hybrid. None of the contributing structures for reaction at a meta position places positive charges on adjacent atoms. As a consequence, resonance stabilization of the cation formed by reaction at a meta position is greater than that for the cation formed by reaction at a para (or ortho) position. Stated alternatively, the activation energy for reaction at a meta position is less than that for reaction at a para position.

A comparison of the entries in Table 9.1 shows that almost all ortho–para directing groups have an unshared pair of electrons on the atom bonded to the aromatic ring. Thus, the directing effect of most of these groups is due primarily to the ability of the atom bonded to the ring to delocalize further the positive charge on the cation intermediate.

The fact that alkyl groups are also ortho–para directing indicates that they, too, help to stabilize the cation intermediate. In Section 5.3A, we saw that alkyl groups stabilize carbocation intermediates and that the order of stability of carbocations is 3° > 2° > 1° > methyl. Just as alkyl groups stabilize the cation intermediates formed in reactions of alkenes, they also stabilize the carbocation intermediates formed in electrophilic aromatic substitutions.

To summarize, any substituent on an aromatic ring that further stabilizes the cation intermediate directs ortho–para, and any group that destabilizes the cation intermediate directs meta.

EXAMPLE 9.8

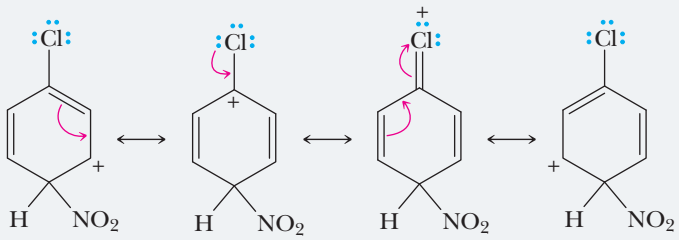
Draw contributing structures formed during the para nitration of chlorobenzene, and show how chlorine participates in directing the incoming nitronium ion to ortho–para positions.

STRATEGY

Draw the intermediate that is formed initially from para attack of the electrophile. Then draw a contributing structure by moving electrons from the pi bond adjacent to the positive charge. Repeat for all contributing structures until all resonance possibilities have been exhausted. *Note:* Be sure to look for resonance possibilities outside of the benzene ring.

SOLUTION

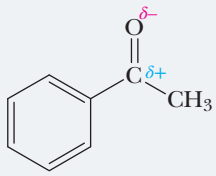
Contributing structures (a), (b), and (d) place the positive charge on atoms of the ring, while contributing structure (c) places it on chlorine and thus creates additional resonance stabilization for the cation intermediate:



See problem 9.29

PROBLEM 9.8

Because the electronegativity of oxygen is greater than that of carbon, the carbon of a carbonyl group bears a partial positive charge, and its oxygen bears a partial negative charge. Using this information, show that a carbonyl group is meta directing:



C. Theory of Activating–Deactivating Effects

We account for the activating–deactivating effects of substituent groups by a combination of resonance and inductive effects:

1. Any resonance effect, such as that of —NH_2, —OH, and —OR, which delocalizes the positive charge of the cation intermediate lowers the activation energy for its formation and is activating toward further electrophilic aromatic substitution. That is, these groups increase the rate of electrophilic aromatic substitution, compared with the rate at which benzene itself reacts.

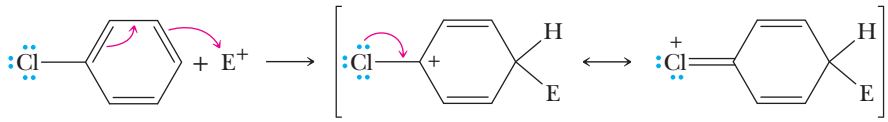
2. Any resonance or inductive effect, such as that of —NO_2, —$\overset{\overset{O}{\|}}{C}$—, —$SO_3H$, —$NR_3^+$, —$CCl_3$, and —$CF_3$, which decreases electron density on the ring, deactivates the ring to further substitution. That is, these groups decrease the rate of further electrophilic aromatic substitution, compared with the rate at which benzene itself reacts.

3. Any inductive effect (such as that of —CH_3 or another alkyl group), which releases electron density toward the ring, activates the ring toward further substitution.

In the case of the halogens, the resonance and inductive effects operate in opposite directions. As Table 9.1 shows, the halogens are ortho–para directing, but, unlike other ortho–para directors listed in the table, the halogens are weakly deactivating. These observations can be accounted for in the following way.

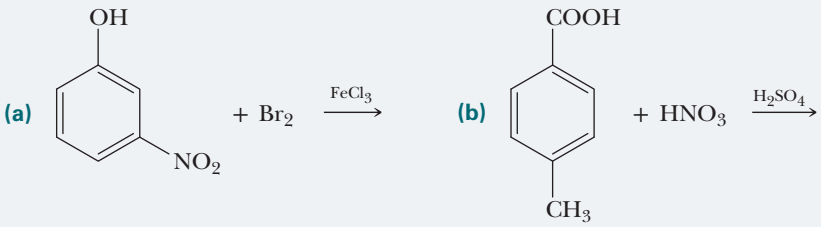
1. *The inductive effect of halogens.* The halogens are more electronegative than carbon and have an electron-withdrawing inductive effect. Aryl halides, therefore, react more slowly in electrophilic aromatic substitution than benzene does.

2. *The resonance effect of halogens.* A halogen ortho or para to the site of electrophilic attack stabilizes the cation intermediate by delocalization of the positive charge:



EXAMPLE 9.9

Predict the product of each electrophilic aromatic substitution.

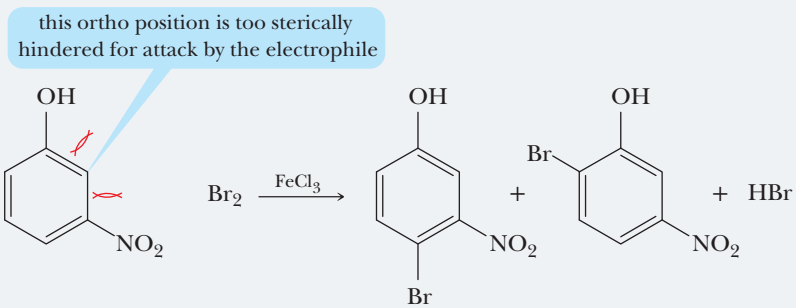


STRATEGY

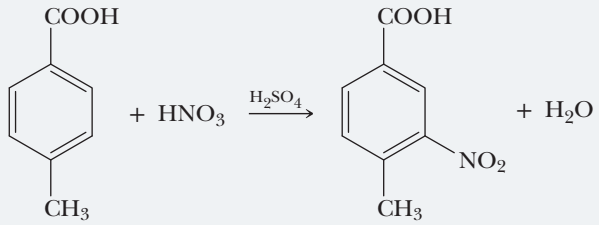
Determine the activating and deactivating effect of each group. The key to predicting the orientation of further substitution on a disubstituted arene is that ortho–para directing groups are always better at activating the ring toward further substitution than meta directing groups (Table 9.1). This means that, when there is competition between ortho–para directing and meta directing groups, the ortho–para group wins.

SOLUTION

(a) The ortho–para directing and activating —OH group determines the position of bromination. Bromination between the —OH and —NO_2 groups is only a minor product because of steric hindrance to attack of bromine at this position:



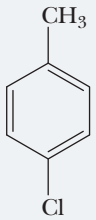
(b) The ortho–para directing and activating methyl group determines the position of nitration:

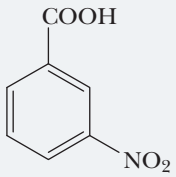


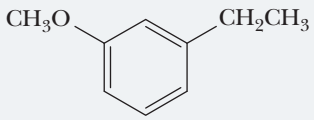
See problems 9.24–9.26, 9.31, 9.32, 9.42–9.44, 9.46, 9.47

PROBLEM 9.9

Predict the product of treating each compound with HNO_3/H_2SO_4:

(a) 

(b) 

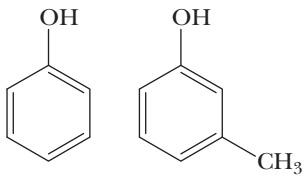
(c) 

9.8 What Are Phenols?

A. Structure and Nomenclature

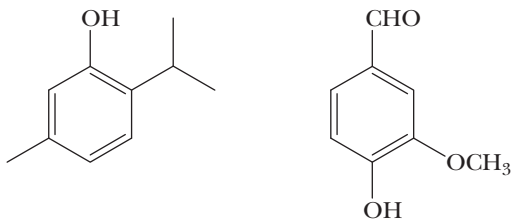
Phenol A compound that contains an —OH group bonded to a benzene ring.

The functional group of a **phenol** is a hydroxyl group bonded to a benzene ring. We name substituted phenols either as derivatives of phenol or by common names:



Phenol | 3-Methylphenol (*m*-Cresol) | 1,2-Benzenediol (Catechol) | 1,3-Benzenediol (Resorcinol) | 1,4-Benzenediol (Hydroquinone)

Phenols are widely distributed in nature. Phenol itself and the isomeric cresols (*o*-, *m*-, and *p*-cresol) are found in coal tar. Thymol and vanillin are important constituents of thyme and vanilla beans, respectively:

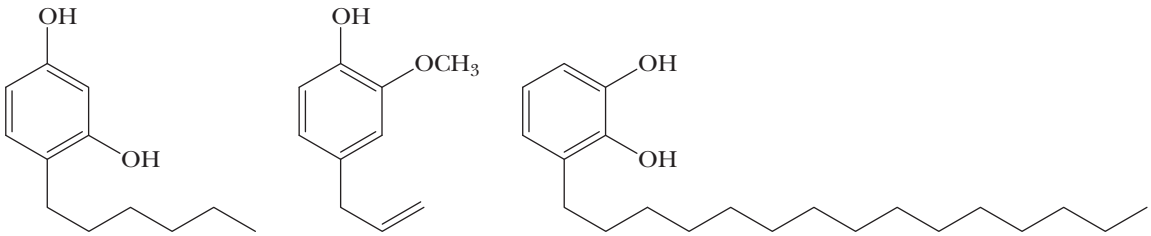


2-Isopropyl-5-methylphenol (Thymol) | 4-Hydroxy-3-methoxybenzaldehyde (Vanillin)

Eriko Koga/Digital Vision/Getty Images, Inc

Thymol is a constituent of garden thyme, *Thymus vulgaris*.

Phenol, or carbolic acid, as it was once called, is a low-melting solid that is only slightly soluble in water. In sufficiently high concentrations, it is corrosive to all kinds of cells. In dilute solutions, phenol has some antiseptic properties and was introduced into the practice of surgery by Joseph Lister, who demonstrated his technique of aseptic surgery in the surgical theater of the University of Glasgow School of Medicine in 1865. Nowadays, phenol has been replaced by antiseptics that are both more powerful and have fewer undesirable side effects. Among these is hexylresorcinol, which is widely used in nonprescription preparations as a mild antiseptic and disinfectant.



Hexylresorcinol Eugenol Urushiol

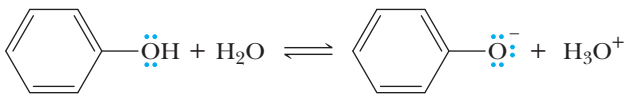
Eugenol, which can be isolated from the flower buds (cloves) of *Eugenia aromatica*, is used as a dental antiseptic and analgesic. Urushiol is the main component in the irritating oil of poison ivy.

Charles D. Winters

Poison ivy.

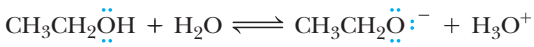
B. Acidity of Phenols

Phenols and alcohols both contain an —OH group. We group phenols as a separate class of compounds, however, because their chemical properties are quite different from those of alcohols. One of the most important of these differences is that phenols are significantly more acidic than are alcohols. Indeed, the acid ionization constant for phenol is 10^6 times larger than that of ethanol!



Phenol Phenoxide ion

$K_a = 1.1 \times 10^{-10}$ $pK_a = 9.95$



Ethanol Ethoxide ion

$K_a = 1.3 \times 10^{-16}$ $pK_a = 15.9$

Another way to compare the relative acid strengths of ethanol and phenol is to look at the hydrogen ion concentration and pH of a 0.1-M aqueous solution of each (Table 9.2). For comparison, the hydrogen ion concentration and pH of 0.1 M HCl are also included.

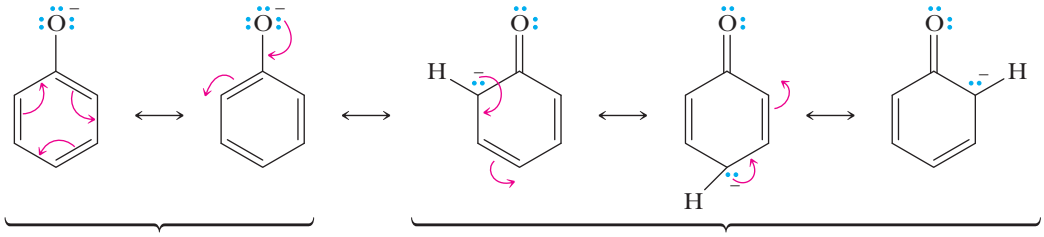
In aqueous solution, alcohols are neutral substances, and the hydrogen ion concentration of 0.1 M ethanol is the same as that of pure water. A 0.1-M solution of phenol is slightly acidic and has a pH of 5.4. By contrast, 0.1 M HCl, a strong acid (completely ionized in aqueous solution), has a pH of 1.0.

The greater acidity of phenols compared with alcohols results from the greater stability of the phenoxide ion compared with an alkoxide ion. The negative charge on the phenoxide ion is delocalized by resonance. The two contributing structures on the left for the phenoxide ion place the negative charge on oxygen, while the three on the right place the negative charge on the ortho and para positions of the ring. Thus, in the resonance hybrid, the negative charge of the phenoxide ion is delocalized over four atoms,

TABLE 9.2 Relative Acidities of 0.1-M Solutions of Ethanol, Phenol, and HCl

Acid Ionization Equation	$[H^+]$	pH
$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+$	1×10^{-7}	7.0
$C_6H_5OH + H_2O \rightleftharpoons C_6H_5O^- + H_3O^+$	3.3×10^{-6}	5.4
$HCl + H_2O \rightleftharpoons Cl^- + H_3O^+$	0.1	1.0

which stabilizes the phenoxide ion realtive to an alkoxide ion, for which no delocalization is possible:

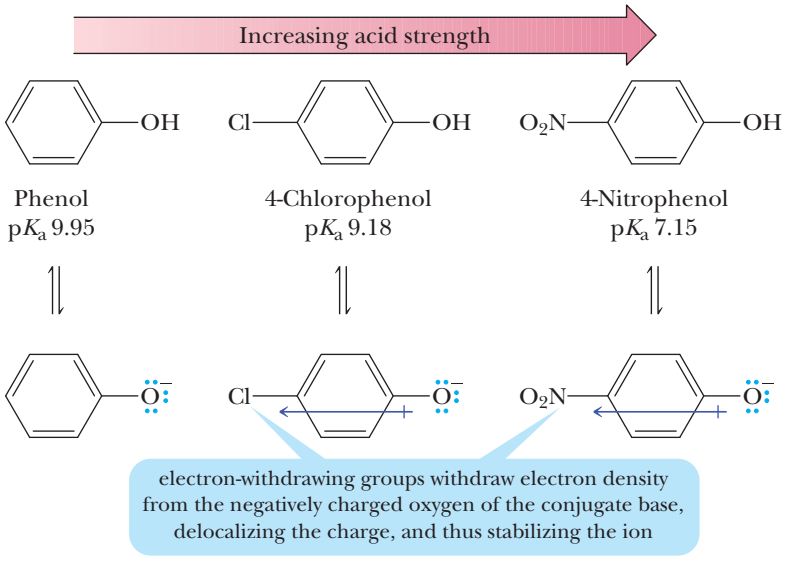


These two Kekulé structures are equivalent

These three contributing structures delocalize the negative charge onto carbon atoms of the ring

Note that, although the resonance model gives us a way of understanding why phenol is a stronger acid than ethanol, it does not provide us with any quantitative means of predicting just how much stronger an acid it might be. To find out how much stronger one acid is than another, we must determine their pK_a values experimentally and compare them.

Ring substituents, particularly halogen and nitro groups, have marked effects on the acidities of phenols through a combination of inductive and resonance effects. Because the halogens are more electronegative than carbon, they withdraw electron density from the negatively charged oxygen in the conjugate base, stabilizing the phenoxide ion. Nitro groups have greater electron-withdrawing ability than halogens and thus have a greater stabilizing effect on the phenoxide ion, making nitrophenol even more acidic than chlorophenol.



EXAMPLE 9.10

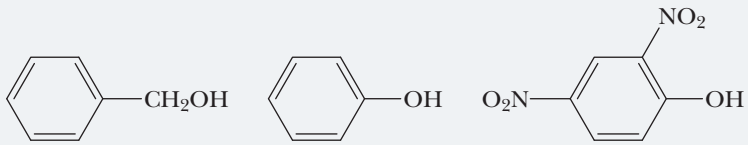
Arrange these compounds in order of increasing acidity: 2,4-dinitrophenol, phenol, and benzyl alcohol.

STRATEGY

Draw each conjugate base. Then determine which conjugate base is more stable using the principles of resonance and inductive effects. The more stable the conjugate base, the more acidic the acid from which it was generated.

SOLUTION

Benzyl alcohol, a primary alcohol, has a pK_a of approximately 16–18 (Section 8.2A). The pK_a of phenol is 9.95. Nitro groups are electron withdrawing and increase the acidity of the phenolic —OH group. In order of increasing acidity, these compounds are:



Benzyl alcohol
pK_a 16–18

Phenol
pK_a 9.95

2,4-Dinitrophenol
pK_a 3.96

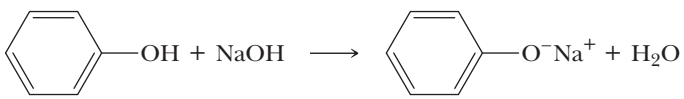
See problems 9.36–9.38

PROBLEM 9.10

Arrange these compounds in order of increasing acidity: 2,4-dichlorophenol, phenol, cyclohexanol.

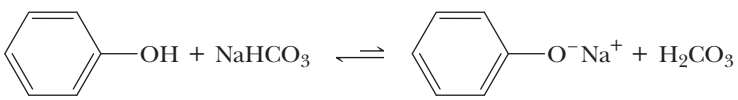
C. Acid–Base Reactions of Phenols

Phenols are weak acids and react with strong bases, such as NaOH, to form water-soluble salts:



Phenol	Sodium hydroxide	Sodium phenoxide	Water
pK_a 9.95			pK_a 15.7
(stronger acid)	(stronger base)	(weaker base)	(weaker acid)

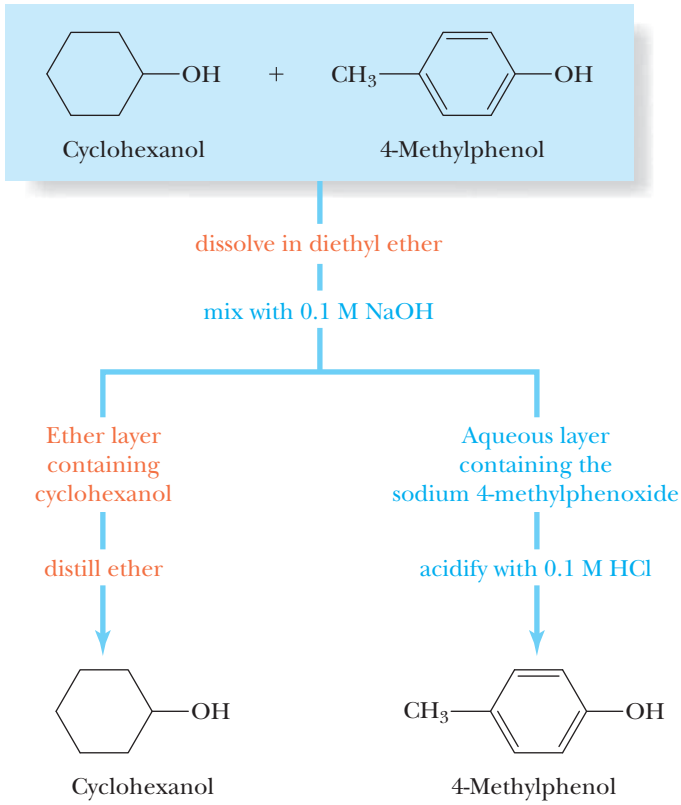
Most phenols do not react with weaker bases, such as sodium bicarbonate, and do not dissolve in aqueous sodium bicarbonate. Carbonic acid is a stronger acid than most phenols, and, consequently, the equilibrium for their reaction with bicarbonate ion lies far to the left (see Section 2.4):



Phenol	Sodium bicarbonate	Sodium phenoxide	Carbonic acid
pK_a 9.95			pK_a 6.36
(weaker acid)	(weaker base)	(stronger base)	(stronger acid)

The fact that phenols are weakly acidic, whereas alcohols are neutral, provides a convenient way to separate phenols from water-insoluble alcohols. Suppose that we want to separate 4-methylphenol from cyclohexanol. Each is only slightly soluble in water; therefore, they cannot be separated on the basis of their water solubility. They can be separated, however, on the basis of their difference in acidity. First, the mixture of the two is dissolved in diethyl ether or some other water-immiscible solvent. Next, the ether solution is placed in a separatory funnel and shaken with dilute aqueous NaOH. Under these conditions, 4-methylphenol reacts with NaOH to give sodium 4-methylphenoxide, a water-soluble salt. The upper layer in the separatory funnel is now diethyl ether (density 0.74 g/cm^3), containing only dissolved cyclohexanol. The lower aqueous layer contains dissolved sodium 4-methylphenoxide. The layers are separated, and distillation of the ether (bp 35°C) leaves pure cyclohexanol (bp 161°C). Acidification of the aqueous phase with 0.1 M HCl or another strong acid converts sodium 4-methylphenoxide to 4-methylphenol, which is insoluble in water and can be

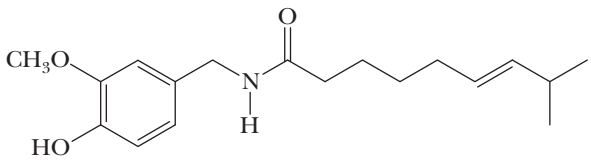
extracted with ether and recovered in pure form. The following flowchart summarizes these experimental steps:



Chemical Connections 9B

CAPSAICIN, FOR THOSE WHO LIKE IT HOT

Capsaicin, the pungent principle from the fruit of various peppers (*Capsicum* and *Solanaceae*), was isolated in 1876, and its structure was determined in 1919:



Capsaicin
(from various types of peppers)

The inflammatory properties of capsaicin are well known; the human tongue can detect as little as one drop of it in 5 L of water. Many of us are familiar with the burning sensation in the mouth and sudden tearing in the eyes caused by a good dose of hot chili peppers. Capsaicin-containing extracts from these flaming foods are also used in sprays to ward off dogs or other animals that might nip at your heels while you are running or cycling.

Ironically, capsaicin is able to cause pain and relieve it as well. Currently, two capsaicin-containing creams, Mioton and Zostrix®, are prescribed to treat the burning pain associated with postherpetic neuralgia, a complication of shingles. They are also prescribed for diabetics, to relieve persistent foot and leg pain.

The mechanism by which capsaicin relieves pain is not fully understood. It has been suggested that, after it is applied, the nerve endings in the area responsible for the transmission of pain remain temporarily numb. Capsaicin remains bound to specific receptor sites on these pain-transmitting neurons, blocking them from further action. Eventually, capsaicin is removed from the receptor sites, but in the meantime, its presence provides needed relief from pain.

Question

Would you predict capsaicin to be more soluble in water or more soluble in 1-octanol?

Would your prediction remain the same if capsaicin were first treated with a molar equivalent of NaOH?

D. Phenols as Antioxidants

An important reaction in living systems, foods, and other materials that contain carbon–carbon double bonds is **autoxidation**—that is, oxidation requiring oxygen and no other reactant. If you open a bottle of cooking oil that has stood for a long time, you will notice a hiss of air entering the bottle. This sound occurs because the consumption of oxygen by autoxidation of the oil creates a negative pressure inside the bottle.

Cooking oils contain esters of polyunsaturated fatty acids. You need not worry now about what esters are; we will discuss them in Chapter 14. The important point here is that all vegetable oils contain fatty acids with long hydrocarbon chains, many of which have one or more carbon–carbon double bonds. (See Problem 4.44 for the structures of three of these fatty acids.) Autoxidation takes place at a carbon adjacent to a double bond—that is, at an **allylic carbon**.

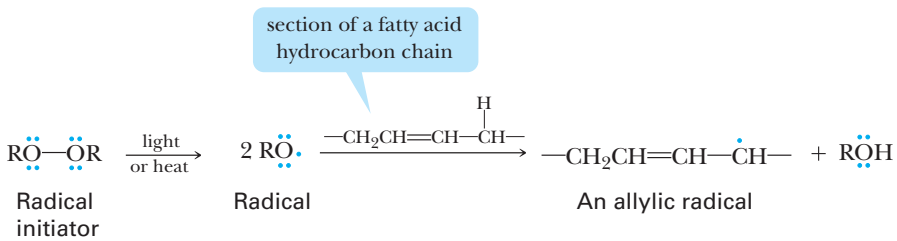
Autoxidation is a radical chain process that converts an R—H group into an R—O—O—H group, called a *hydroperoxide*. The process begins when energy in the form of heat or light causes a molecule with a weak bond to form two **radicals**, atoms, or molecules with an unpaired electron. This step is known as **chain initiation**. In the laboratory, small amounts of compounds such as peroxides, ROOR, are used as initiators because they are easily converted to RO· radi-

Although we represent molecular oxygen with the Lewis structure shown in (a), oxygen has long been known to exist and behave as a diradical, as shown in (b).

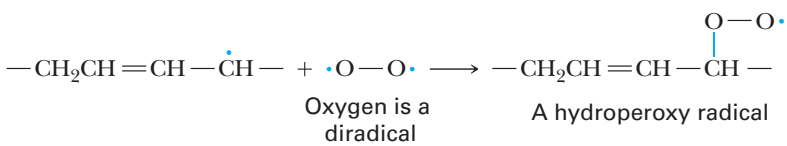
Mechanism

Autoxidation

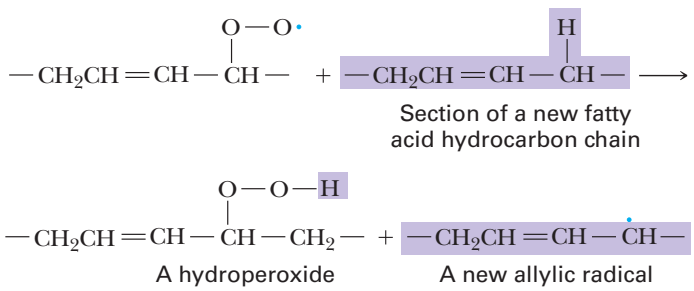
STEP 1: *Chain Initiation—Formation of a Radical from a Nonradical Compound.*
The radical generated from the exposure of the initiator to light or heat causes the removal of a hydrogen atom (H·) adjacent to a C═C double bond to give an allylic radical:



STEP 2A: *Chain Propagation—Reaction of a Radical and Oxygen to Form a New Radical.*
The allylic radical reacts with oxygen, itself a diradical, to form a hydroperoxy radical. The new covalent bond of the hydroperoxy radical forms by the combination of one electron from the allylic radical and one electron from the oxygen diradical:



STEP 2B: *Chain Propagation—Reaction of a Radical and a Molecule to Form a New Radical.*
The hydroperoxy radical removes an allylic hydrogen atom (H·) from a new fatty acid hydrocarbon chain to complete the formation of a hydroperoxide and, at the same time, produce a new allylic radical:



Charles D. Winters

Butylated hydroxytoluene (BHT) is often used as an antioxidant in baked goods to "retard spoilage."

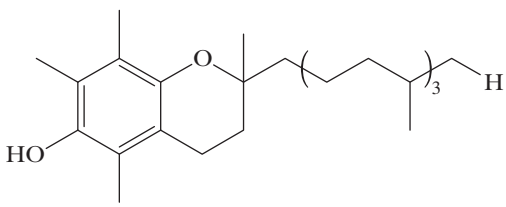
cals by light or heat. Scientists are still unsure precisely what compounds act as initiators in nature. Once a radical is generated, it reacts with a molecule by removing the hydrogen atom together with one of its electrons (H·) from an allylic carbon. The carbon losing the H· now has only seven electrons in its valence shell, one of which is unpaired.

The most important point about the pair of chain propagation steps is that they form a continuous cycle of reactions. The new radical formed in Step 2b next reacts with another molecule of O_2 in Step 2a to give a new hydroperoxy radical, which then reacts with a new hydrocarbon chain to repeat Step 2b, and so forth. This cycle of propagation steps repeats over and over in a chain reaction. Thus, once a radical is generated in Step 1, the cycle of propagation steps may repeat many thousands of times, generating thousands and thousands of hydroperoxide molecules. The number of times the cycle of chain propagation steps repeats is called the **chain length**.

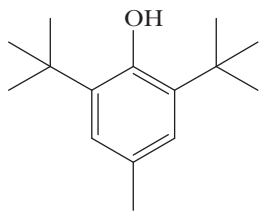
Hydroperoxides themselves are unstable and, under biological conditions, degrade to short-chain aldehydes and carboxylic acids with unpleasant "rancid" smells. These odors may be familiar to you if you have ever smelled old cooking oil or aged foods that contain polyunsaturated fats or oils. A similar formation of hydroperoxides in the low-density lipoproteins deposited on the walls of arteries leads to cardiovascular disease in humans. In addition, many effects of aging are thought to be the result of the formation and subsequent degradation of hydroperoxides.

Fortunately, nature has developed a series of defenses, including the phenol vitamin E, ascorbic acid (vitamin C), and glutathione, against the formation of destructive hydroperoxides. The compounds that defend against hydroperoxides are "nature's scavengers." Vitamin E, for example, inserts itself into either Step 2a or 2b, donates an H· from its phenolic —OH group to the allylic radical, and converts the radical to its original hydrocarbon chain. Because the vitamin E radical is stable, it breaks the cycle of chain propagation steps, thereby preventing the further formation of destructive hydroperoxides. While some hydroperoxides may form, their numbers are very small and they are easily decomposed to harmless materials by one of several enzyme-catalyzed reactions.

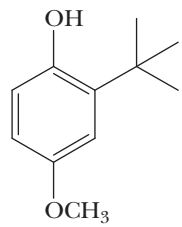
Unfortunately, vitamin E is removed in the processing of many foods and food products. To make up for this loss, phenols such as BHT and BHA are added to foods to "retard [their] spoilage" (as they say on the packages) by autoxidation:



Vitamin E



*B*utylated *h*ydroxy-*t*oluene (BHT)



*B*utylated *h*ydroxy-*a*nisole (BHA)

Similar compounds are added to other materials, such as plastics and rubber, to protect them against autoxidation. The protective properties of phenols may explain why the health benefits of foods such as green tea, wine, and blueberries (each of which contains large amounts of phenolic compounds) have been lauded by nutritionists and others in the medical community.

SUMMARY OF KEY QUESTIONS

9.1 What Is the Structure of Benzene?

- **Benzene** is a molecule with a high degree of unsaturation possessing the molecular formula C_6H_6. Each carbon has a single unhybridized 2*p* orbital that contains one electron. These six 2*p* orbitals lie perpendicular to the plane of the ring and overlap to form a continuous pi cloud encompassing all six carbons.
- Benzene and its alkyl derivatives are classified as **aromatic hydrocarbons,** or **arenes.**

9.2 What Is Aromaticity?

- According to the **Hückel criteria for aromaticity**, a cyclic compound is aromatic if it (1) has one 2*p* orbital on each atom of the ring, (2) is planar so that overlap of all *p* orbitals of the ring is continuous or nearly so, and (3) has 2, 6, 10, 14, and so on, pi electrons in the overlapping system of *p* orbitals (i.e., it has $4n + 2\pi$ electrons).
- A **heterocyclic aromatic compound** contains one or more atoms other than carbon in an aromatic ring.

9.3 How Are Benzene Compounds Named, and What Are Their Physical Properties?

- Aromatic compounds are named by the IUPAC system. The common names **toluene**, **xylene**, **styrene**, **phenol**, **aniline**, **benzaldehyde**, and **benzoic acid** are retained.
- The C_6H_5— group is named **phenyl**, and the $C_6H_5CH_2$— group is named **benzyl**.
- To locate two substituents on a benzene ring, either number the atoms of the ring or use the locators **ortho (*o*)**, **meta (*m*)**, and **para (*p*)**.
- **Polynuclear aromatic hydrocarbons** contain two or more fused benzene rings.

9.4 What Is the Benzylic Position, and How Does It Contribute to Benzene Reactivity?

- The **benzylic position** is the carbon of an alkyl substituent immediately bonded to the benzene ring.
- The benzylic position of a benzene ring can be oxidized by chromic acid without affecting any of the benzene ring atoms.

9.5 What Is Electrophilic Aromatic Substitution?

- A characteristic reaction of aromatic compounds is **electrophilic aromatic substitution**, which involves the substitution of one of the ring hydrogens of benzene for an electrophilic reagent.
- The five types of electrophilic aromatic substitution discussed here are **nitration**, **halogenation**, **sulfonation**, **Friedel–Crafts alkylation**, and **Friedel–Crafts acylation**.

9.6 What Is the Mechanism of Electrophilic Aromatic Substitution?

- The mechanism of electrophilic aromatic substitution can be broken down into three common steps: (1) generation of the electrophile, (2) attack of the electrophile on the aromatic ring to give a resonance-stabilized cation intermediate, and (3) proton transfer to a base to regenerate the aromatic ring.
- The five electrophilic aromatic substitution reactions studied here differ in their mechanism of formation of the electrophile (Step 1) and the specific base used to effect the proton transfer to regenerate the aromatic ring (Step 3).

9.7 How Do Existing Substituents on Benzene Affect Electrophilic Aromatic Substitution?

- Substituents on an aromatic ring influence both the rate and site of further substitution.
- Substituent groups that direct an incoming group preferentially to the ortho and para positions are called **ortho–para directors**. Those that direct an incoming group preferentially to the meta positions are called **meta directors**.
- **Activating groups** cause the rate of further substitution to be faster than that for benzene; **deactivating groups** cause it to be slower than that for benzene.
- A mechanistic rationale for directing effects is based on the degree of resonance stabilization of the possible cation intermediates formed upon reaction of the aromatic ring and the electrophile.
- Groups that stabilize the cation intermediate are ortho–para directors; groups that destabilize it are deactivators and meta directors.

9.8 What Are Phenols?

- The functional group of a **phenol** is an —OH group bonded to a benzene ring.
- Phenol and its derivatives are weak acids, with pK_a approximately 10.0, but are considerably stronger acids than alcohols, with pK_a 16–18.
- Various phenols are used to prevent autoxidation, a radical chain process that converts an R—H group into an R—O—O—H (hydroperoxide) group and causes spoilage in foods.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. The mechanism of electrophilic aromatic substitution involves three steps: generation of the electrophile, attack of the electrophile on the benzene ring, and proton transfer to regenerate the ring. (9.6)

2. The C—C double bonds in benzene do not undergo the same addition reactions that the C—C double bonds in alkenes undergo. (9.1)

3. Friedel–Crafts acylation is not subject to rearrangements. (9.5)

4. An aromatic compound is planar, possesses a 2*p* orbital on every atom of the ring, and contains either 4, 8, 12, 16, and so on, pi electrons. (9.2)

5. When naming disubstituted benzenes, the locators para, meta, and ortho refer to substituents that are 1,2, 1,3, and 1,4, respectively. (9.3)

6. The electrophile in the chlorination or bromination of benzene is an ion pair containing a chloronium or bromonium ion. (9.6)

7. An ammonium group (—NH_3^+) on a benzene ring will direct an attacking electrophile to a meta position. (9.7)

8. Reaction of chromic acid, H_2CrO_4, with a substituted benzene always oxidizes every alkyl group at the benzylic position to a carboxyl group. (9.4)

9. Benzene consists of two contributing structures that rapidly interconvert between each other. (9.1)

10. The electrophile in the nitration of benzene is the nitrate ion. (9.6)

11. A benzene ring with an —OH bonded to it is referred to as "phenyl." (9.3)

12. Friedel–Crafts alkylation of a primary haloalkane with benzene will always result in a new bond between benzene and the carbon that was bonded to the halogen. (9.5)

13. Resonance energy is the energy a ring contains due to the stability afforded it by its contributing structures. (9.1)

14. A phenol will react quantitatively with NaOH. (9.8)

15. The use of a haloalkane and $AlCl_3$ is the only way to synthesize an alkylbenzene. (9.6)

16. Phenols are more acidic than alcohols. (9.8)

17. Substituents of polysubstituted benzene rings can be numbered according to their distance from the substituent that imparts a special name to the compound. (9.3)

18. If a benzene ring contains both a weakly activating group and a strongly deactivating group, the strongly deactivating group will direct the attack of an electrophile. (9.7)

19. Oxygen, O_2, can be considered a diradical. (9.8)

20. The contributing structures for the attack of an electrophile to the ortho position of aniline are more stable than those for the attack at the meta position. (9.7)

21. A deactivating group will cause its benzene ring to react slower than benzene itself. (9.7)

22. Friedel–Crafts alkylation is promoted by the presence of electron-withdrawing groups. (9.5)

23. Autoxidation takes place at allylic carbons. (9.8)

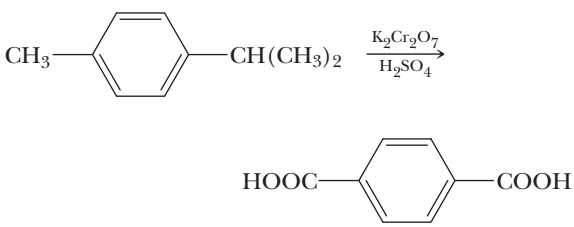
24. The contributing structures for the attack of an electrophile to the meta position of nitrobenzene are more stable than those for the attack at the ortho or para position. (9.7)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

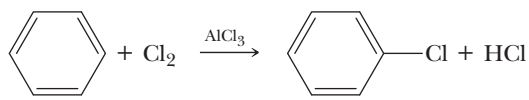
Answers: (1) T (2) T (3) T (4) F (5) F (6) T (7) T (8) F (9) F (10) F (11) F (12) F (13) F (14) T (15) F (16) T (17) T (18) F (19) T (20) T (21) T (22) F (23) T (24) T

KEY REACTIONS

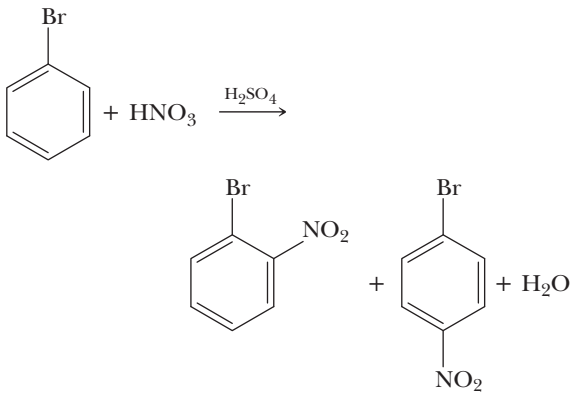
1. **Oxidation at a Benzylic Position (Section 9.4)**
A benzylic carbon bonded to at least one hydrogen is oxidized to a carboxyl group:



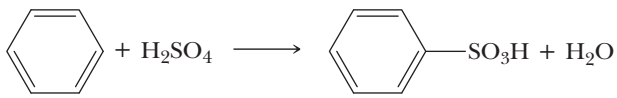
2. **Chlorination and Bromination (Section 9.6A)**
The electrophile is a halonium ion, Cl^+ or Br^+, formed by treating Cl_2 or Br_2 with $AlCl_3$ or $FeCl_3$:



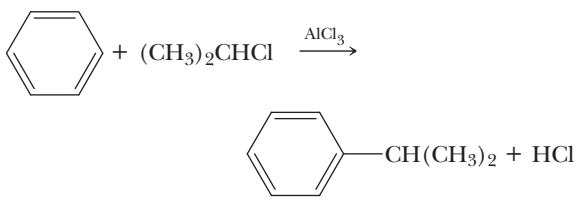
3. Nitration (Section 9.6B)
The electrophile is the nitronium ion, NO_2^+, formed by treating nitric acid with sulfuric acid:



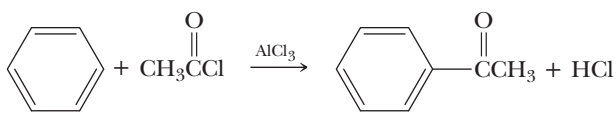
4. Sulfonation (Section 9.6B)
The electrophile is HSO_3^+:



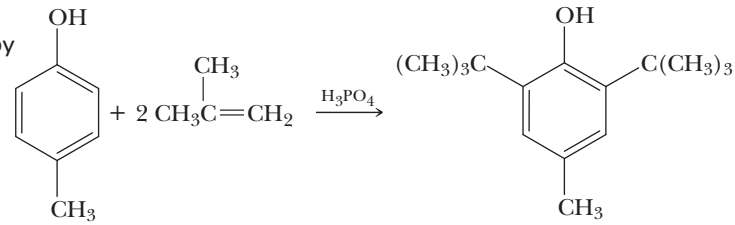
5. Friedel–Crafts Alkylation (Section 9.6C)
The electrophile is an alkyl carbocation formed by treating an alkyl halide with a Lewis acid:



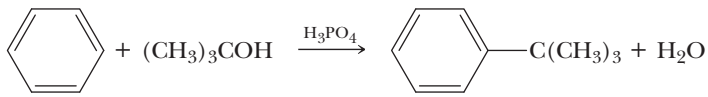
6. Friedel–Crafts Acylation (Section 9.6D)
The electrophile is an acyl cation formed by treating an acyl halide with a Lewis acid:



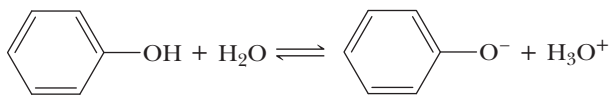
7. Alkylation Using an Alkene (Section 9.6E)
The electrophile is a carbocation formed by treating an alkene with H_2SO_4 or H_3PO_4:



8. Alkylation Using an Alcohol (Section 9.6E)
The electrophile is a carbocation formed by treating an alcohol with H_2SO_4 or H_3PO_4:



9. Acidity of Phenols (Section 9.8B)
Phenols are weak acids:

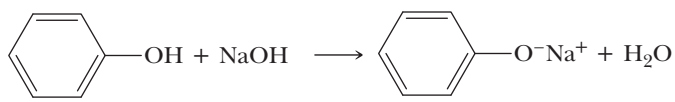


Phenol — Phenoxide ion

$$K_a = 1.1 \times 10^{-10}$$
$$pK_a = 9.95$$

Substitution by electron-withdrawing groups, such as the halogens and the nitro group, increases the acidity of phenols.

10. Reaction of Phenols with Strong Bases (Section 9.8C)
Water-insoluble phenols react quantitatively with strong bases to form water-soluble salts:



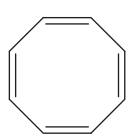
Phenol	Sodium hydroxide	Sodium phenoxide	Water
pK_a 9.95			pK_a 15.7
(stronger acid)	(stronger base)	(weaker base)	(weaker acid)

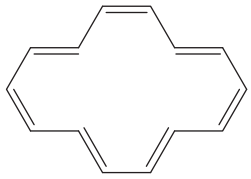
PROBLEMS

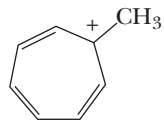
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

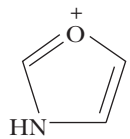
SECTION 9.2 Aromaticity

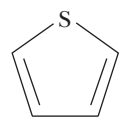
9.11 Which of the following compounds or chemical entities are aromatic? **(See Example 9.1)**

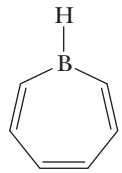
(a) 

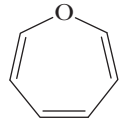
(b) 

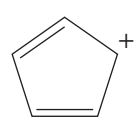
(c) 

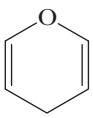
(e) 

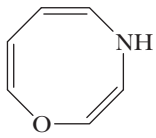
(g) 

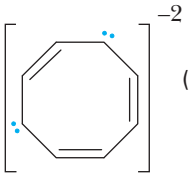
(d) 

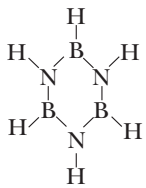
(f) 

(h) 

(i) 

(k) 

(j) 

(l) 

9.12 Explain why cyclopentadiene (pK_a 16) is many orders of magnitude more acidic than cyclopentane (pK_a > 50).

(a) 

Cyclopentadiene

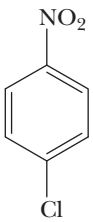
(b) 

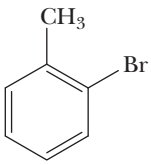
Cyclopentane

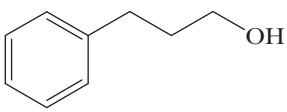
(*Hint:* Draw the structural formula for the anion formed by removing one of the protons on the —CH_2— group, and then apply the Hückel criteria for aromaticity.)

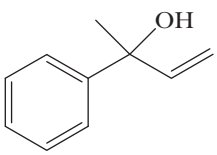
SECTION 9.3 Nomenclature and Structural Formulas

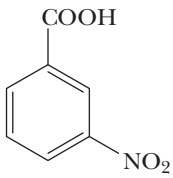
9.13 Name these compounds: **(See Example 9.2)**

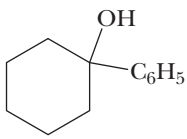
(a) 

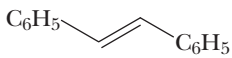
(b) 

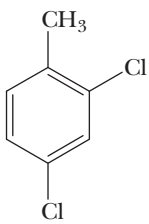
(c) 

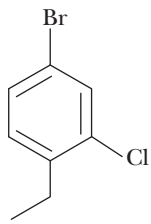
(d) 

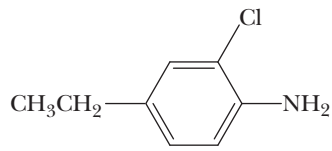
(e) 

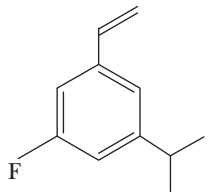
(f) 

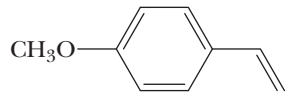
(g) 

(h) 

(i) 

(k) 

(j) 

(l) 

9.14 Draw structural formulas for these compounds: **(See Example 9.2)**

(a) 1-Bromo-2-chloro-4-ethylbenzene
(b) 4-Iodo-1,2-dimethylbenzene
(c) 2,4,6-Trinitrotoluene (TNT)
(d) 4-Phenyl-2-pentanol
(e) *p*-Cresol
(f) 2,4-Dichlorophenol
(g) 1-Phenylcyclopropanol
(h) Styrene (phenylethylene)
(i) *m*-Bromophenol
(j) 2,4-Dibromoaniline
(k) Isobutylbenzene
(l) *m*-Xylene
(m) 4-Bromo-1,2-dichlorobenzene
(n) 5-Fluoro-2-methylphenol
(o) 1-Cyclohexyl-3-ethylbenzene
(p) *m*-Phenylaniline
(q) 3-Methyl-2-vinylbenzoic acid
(r) 2,5-Dimethylanisole

9.15 Show that pyridine can be represented as a hybrid of two equivalent contributing structures.

9.16 Show that naphthalene can be represented as a hybrid of three contributing structures. Show also, by the use of curved arrows, how one contributing structure is converted to the next.

9.17 Draw four contributing structures for anthracene.

SECTIONS 9.5 Electrophilic Aromatic Substitution: Monosubstitution

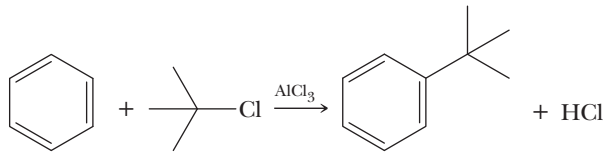
9.18 Draw a structural formula for the compound formed by treating benzene with each of the following combinations of reagents: **(See Examples 9.5, 9.6)**

(a) $CH_3CH_2Cl/AlCl_3$
(b) $CH_2{=}CH_2/H_2SO_4$
(c) CH_3CH_2OH/H_2SO_4
(d) CH_3OCH_3/H_2SO_4

9.19 Show three different combinations of reagents you might use to convert benzene to isopropylbenzene. **(See Examples 9.5, 9.6)**

9.20 How many monochlorination products are possible when naphthalene is treated with $Cl_2/AlCl_3$?

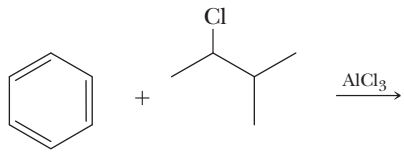
9.21 Write a stepwise mechanism for the following reaction, using curved arrows to show the flow of electrons in each step: **(See Example 9.4)**

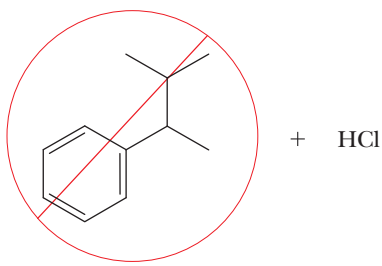


9.22 Write a stepwise mechanism for the preparation of diphenylmethane by treating benzene with dichloromethane in the presence of an aluminum chloride catalyst. **(See Example 9.4)**

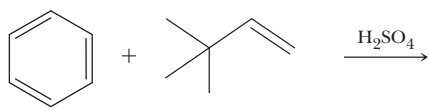
9.23 The following alkylation reactions do not yield the compounds shown as the major product. Predict the major product for each reaction and provide a mechanism for their formation.

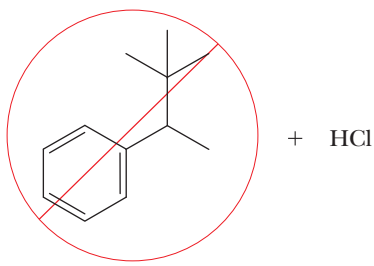
(a)



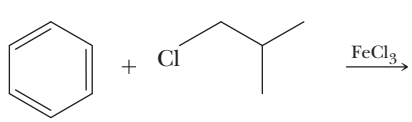


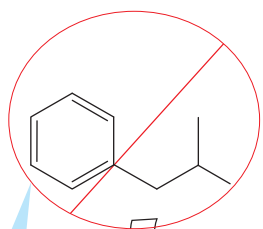
(b)



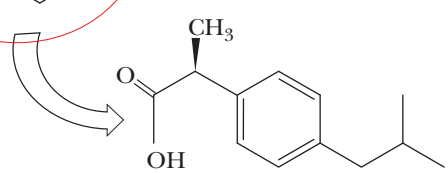


(c)





an important precursor in the synthesis of ibuprofen, which unfortunately cannot be made using these reagents



Ibuprofen

SECTION 9.7 Electrophilic Aromatic Substitution: Substitution Effects

9.24 When treated with $Cl_2/AlCl_3$, 1,2-dimethylbenzene (*o*-xylene) gives a mixture of two products. Draw structural formulas for these products. **(See Examples 9.7, 9.9)**

9.25 How many monosubstitution products are possible when 1,4-dimethylbenzene (*p*-xylene) is treated with $Cl_2/AlCl_3$? When *m*-xylene is treated with $Cl_2/AlCl_3$? **(See Examples 9.7, 9.9)**

9.26 Draw the structural formula for the major product formed upon treating each compound with $Cl_2/AlCl_3$: **(See Examples 9.7, 9.9)**

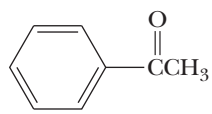
(a) Toluene

(b) Nitrobenzene

(c) Chlorobenzene

(d) *tert*-Butylbenzene

(e)



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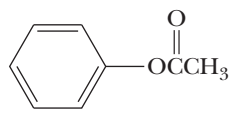

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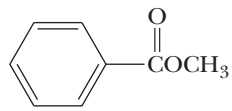

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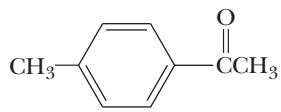

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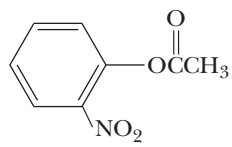
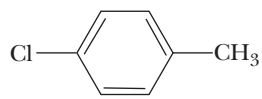


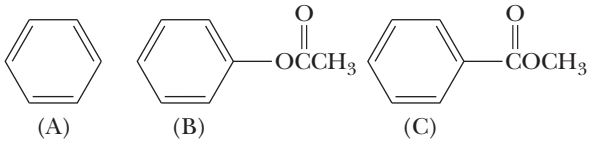
(j)



9.27 Which compound, chlorobenzene or toluene, undergoes electrophilic aromatic substitution more rapidly when treated with $Cl_2/AlCl_3$? Explain and draw structural formulas for the major product(s) from each reaction.

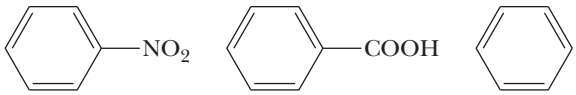
9.28 Arrange the compounds in each set in order of decreasing reactivity (fastest to slowest) toward electrophilic aromatic substitution:

(a)



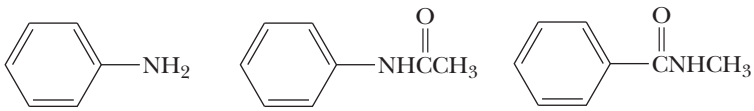
(A) (B) (C)

(b)



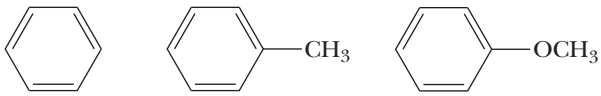
(A) (B) (C)

(c)



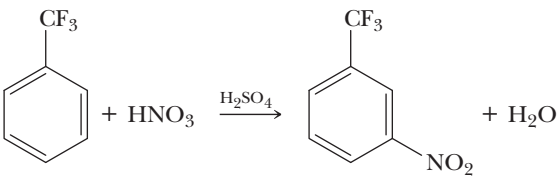
(A) (B) (C)

(d)



(A) (B) (C)

9.29 Account for the observation that the trifluoromethyl group is meta directing, as shown in the following example: **(See Example 9.8)**

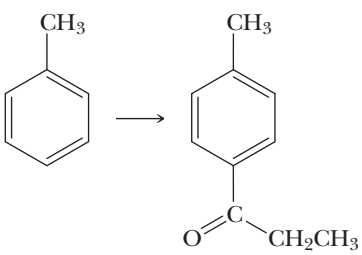


9.30 Show how to convert toluene to these carboxylic acids: **(See Example 9.3)**

(a) 4-Chlorobenzoic acid (b) 3-Chlorobenzoic acid

9.31 Show reagents and conditions that can be used to bring about these conversions: **(See Examples 9.7, 9.9)**

(a)



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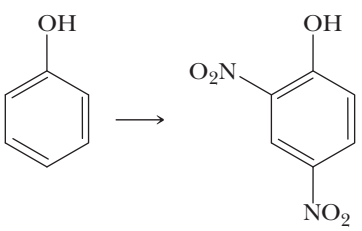

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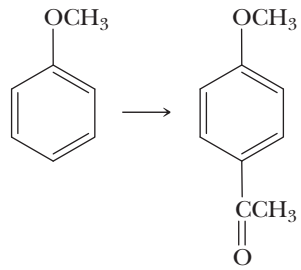

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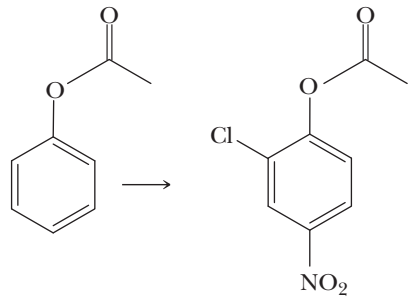
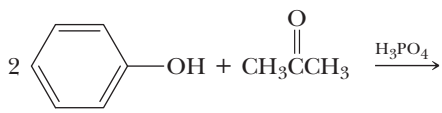
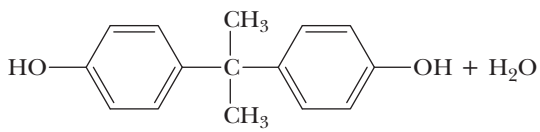


9.32 Propose a synthesis of triphenylmethane from benzene as the only source of aromatic rings. Use any other necessary reagents. **(See Examples 9.7, 9.9)**

***9.33** Reaction of phenol with acetone in the presence of an acid catalyst gives bisphenol A, a compound used in the production of polycarbonate and epoxy resins (Sections 16.4C and 16.4E): **(See Example 9.6)**



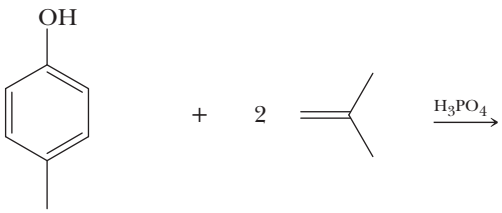
Acetone



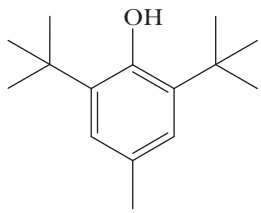
Bisphenol A

Propose a mechanism for the formation of bisphenol A. (*Hint:* The first step is a proton transfer from phosphoric acid to the oxygen of the carbonyl group of acetone.)

***9.34** 2,6-Di-*tert*-butyl-4-methylphenol, more commonly known as butylated hydroxytoluene, or BHT, is used as an antioxidant in foods to "retard spoilage." BHT is synthesized industrially from 4-methylphenol (*p*-cresol) by reaction with 2-methylpropene in the presence of phosphoric acid: **(See Example 9.6)**



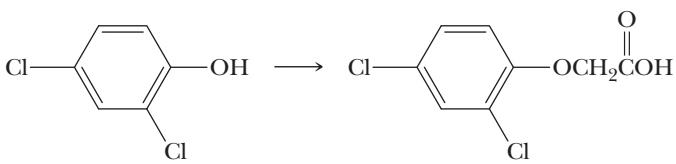
4-Methylphenol 2-Methylpropene



2,6-Di-*tert*-butyl-4-methylphenol
(Butylated hydroxytoluene, BHT)

Propose a mechanism for this reaction.

***9.35** The first herbicide widely used for controlling weeds was 2,4-dichlorophenoxyacetic acid (2,4-D). Show how this compound might be synthesized from 2,4-dichlorophenol and chloroacetic acid, $ClCH_2COOH$:

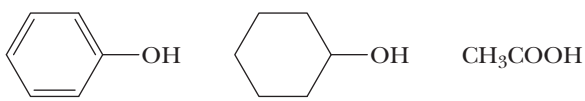


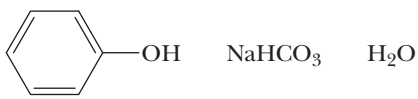
2,4-Dichlorophenol 2,4-Dichlorophenoxyacetic acid (2,4-D)

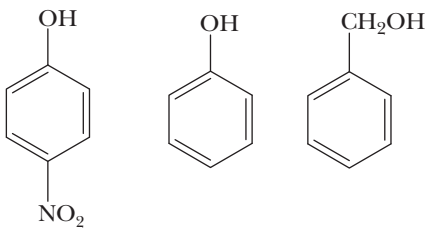
SECTION 9.8 Acidity of Phenols

9.36 Use resonance theory to account for the fact that phenol (pK_a 9.95) is a stronger acid than cyclohexanol (pK_a 18). **(See Example 9.10)**

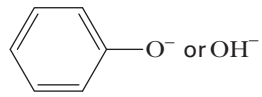
9.37 Arrange the compounds in each set in order of increasing acidity (from least acidic to most acidic): **(See Example 9.10)**

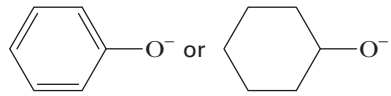
(a) 

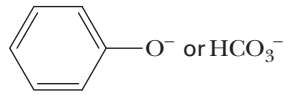
(b) 

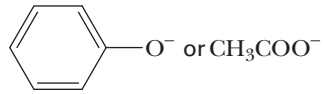
(c) 

9.38 From each pair, select the stronger base: **(See Example 9.10)**

(a) 

(b) 

(c) 

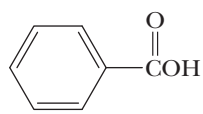
(d) 

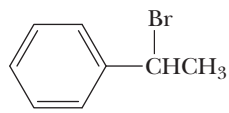
9.39 Account for the fact that water-insoluble carboxylic acids (pK_a 4–5) dissolve in 10% sodium bicarbonate with the evolution of a gas, but water-insoluble phenols (pK_a 9.5–10.5) do not show this chemical behavior.

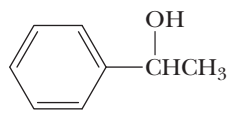
9.40 Describe a procedure for separating a mixture of 1-hexanol and 2-methylphenol (*o*-cresol) and recovering each in pure form. Each is insoluble in water, but soluble in diethyl ether.

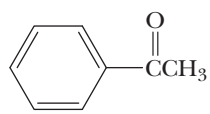
Syntheses

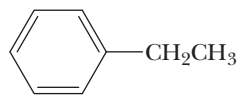
9.41 Using styrene, $C_6H_5CH{=}CH_2$, as the only aromatic starting material, show how to synthesize these compounds. In addition to styrene, use any other necessary organic or inorganic chemicals. Any compound synthesized in one part of this problem may be used to make any other compound in the problem:

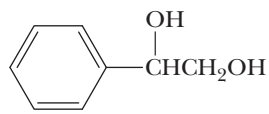
(a) 

(b) 

(c) 

(d) 

(e) 

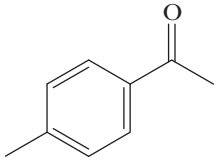
(f) 

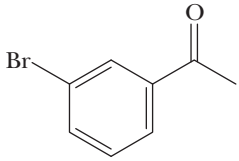
9.42 Show how to synthesize these compounds, starting with benzene, toluene, or phenol as the only sources of aromatic rings. Assume that, in all syntheses, you can separate mixtures of ortho–para products to give the desired isomer in pure form: **(See Examples 9.7, 9.9)**

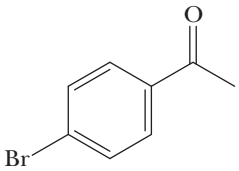
(a) *m*-Bromonitrobenzene
(b) 1-Bromo-4-nitrobenzene
(c) 2,4,6-Trinitrotoluene (TNT)
(d) *m*-Bromobenzoic acid
(e) *p*-Bromobenzoic acid
(f) *p*-Dichlorobenzene
(g) *m*-Nitrobenzenesulfonic acid
(h) 1-Chloro-3-nitrobenzene

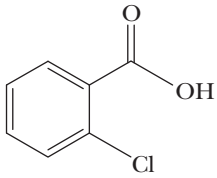
9.43 Show how to synthesize these aromatic ketones, starting with benzene or toluene as the only sources of aromatic rings. Assume that, in all syntheses, mixtures of ortho–para

products can be separated to give the desired isomer in pure form: **(See Examples 9.7, 9.9)**

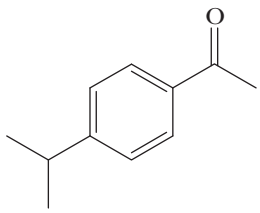
(a) 

(c) 

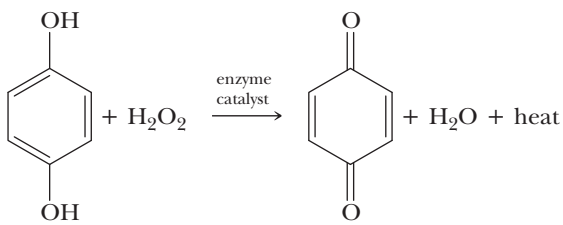
(b) 

(d) 

***9.44** The following ketone, isolated from the roots of several members of the iris family, has an odor like that of violets and is used as a fragrance in perfumes. Describe the synthesis of this ketone from benzene. **(See Examples 9.7, 9.9)**

4-Isopropylacetophenone 

***9.45** The bombardier beetle generates *p*-quinone, an irritating chemical, by the enzyme-catalyzed oxidation of hydroquinone, using hydrogen peroxide as the oxidizing agent. Heat generated in this oxidation produces superheated steam, which is ejected, along with *p*-quinone, with explosive force.

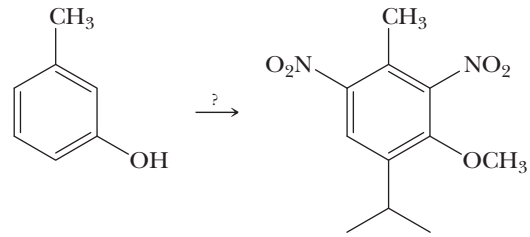


Hydroquinone *p*-Quinone

(a) Balance the equation.

(b) Show that this reaction of hydroquinone is an oxidation.

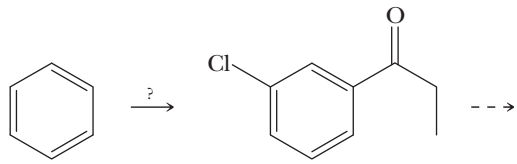
***9.46** Following is a structural formula for musk ambrette, a synthetic musk used in perfumes to enhance and retain fragrance: **(See Examples 9.7, 9.9)**



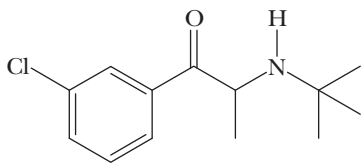
m-Cresol Musk ambrette

Propose a synthesis for musk ambrette from *m*-cresol.

***9.47** (3-Chlorophenyl)propanone is a building block in the synthesis of bupropion, the hydrochloride salt of which is the antidepressant Wellbutrin. During clinical trials, researchers discovered that smokers reported a diminished craving for tobacco after one to two weeks on the drug. Further clinical trials confirmed this finding, and the drug is also marketed under the trade name Zyban® as an aid in smoking cessation. Propose a synthesis for this building block from benzene. (We will see in Section 12.8 how to complete the synthesis of bupropion.) **(See Examples 9.7, 9.9)**



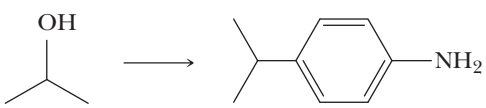
Benzene (3-Chlorophenyl)-1-propanone

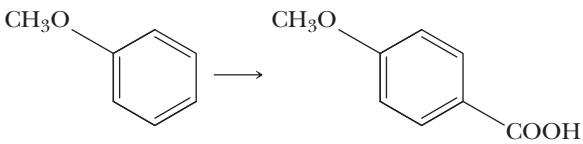


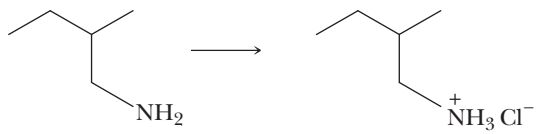
Bupropion (Wellbutrin®, Zyban®)

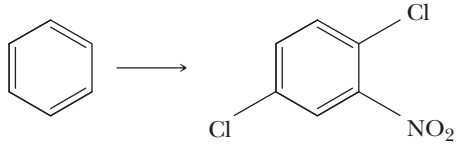
CHEMICAL TRANSFORMATIONS

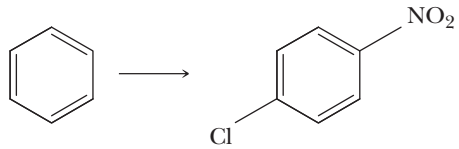
9.48 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.*

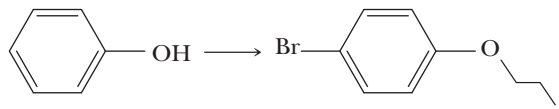
(a) 

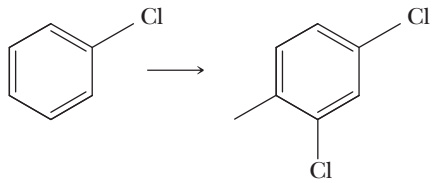
(b) 

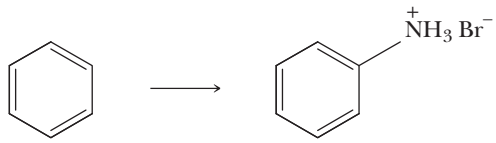
(c) 

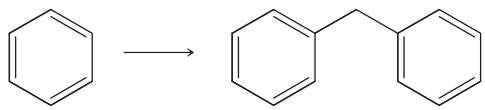
(d) 

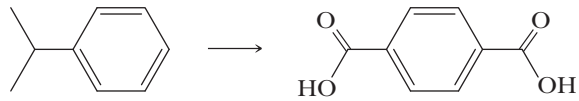
(e) 

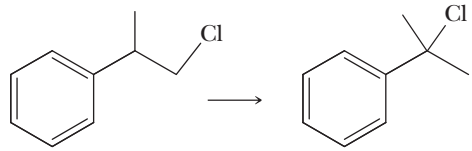
(f) 

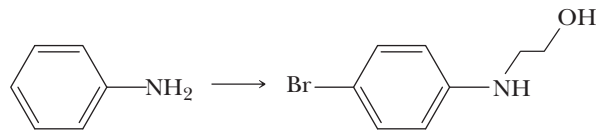
(g) 

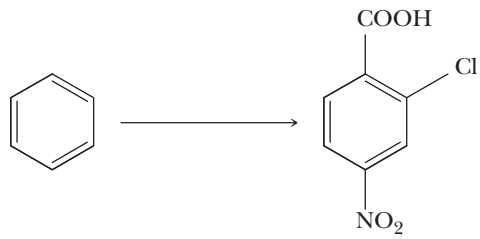
(h) 

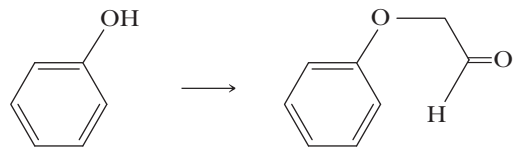
(i) 

(j) 

(k) 

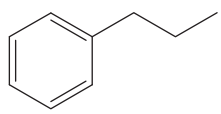
(l) 

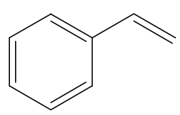
(m) 

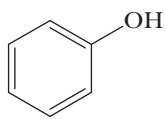
(n) 

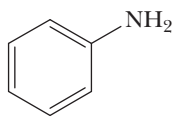
LOOKING AHEAD

9.49 Which of the following compounds can be made directly by using an electrophilic aromatic substitution reaction?

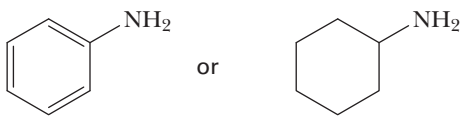
(a) 

(b) 

(c) 

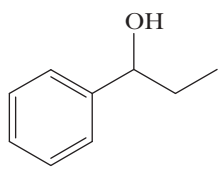
(d) 

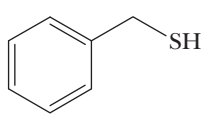
9.50 Which compound is a better nucleophile?

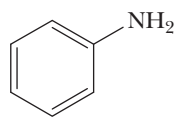


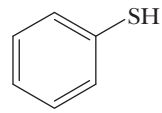
Aniline Cyclohexanamine

9.51 Suggest a reason that the following arenes do not undergo electrophilic aromatic substitution when $AlCl_3$ is used in the reaction:

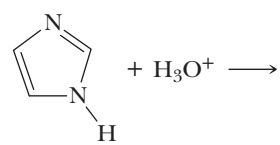
(a) 

(b) 

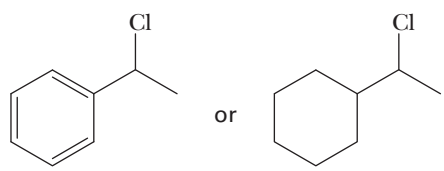
(c) 

(d) 

9.52 Predict the product of the following acid–base reaction:



9.53 Which haloalkane reacts faster in an S_N1 reaction?

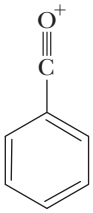


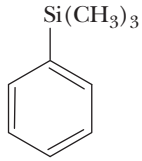
9.54 Which of the following compounds is more basic?

Furan or Tetrahydrofuran

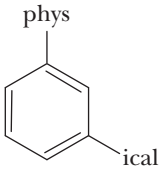
GROUP LEARNING ACTIVITIES

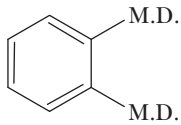
9.55 Following are benzene compounds with substituents we have yet to encounter. As a group, decide whether each ring will be activated or deactivated. Then determine whether each substituent is ortho–para or meta directing by analyzing their intermediates in an electrophilic aromatic substitution reaction.

(a) 

(b) 

9.56 The following structures represent a play on words when named. Can you name them? Can you come up with other funny names?

(a) 

(b) 

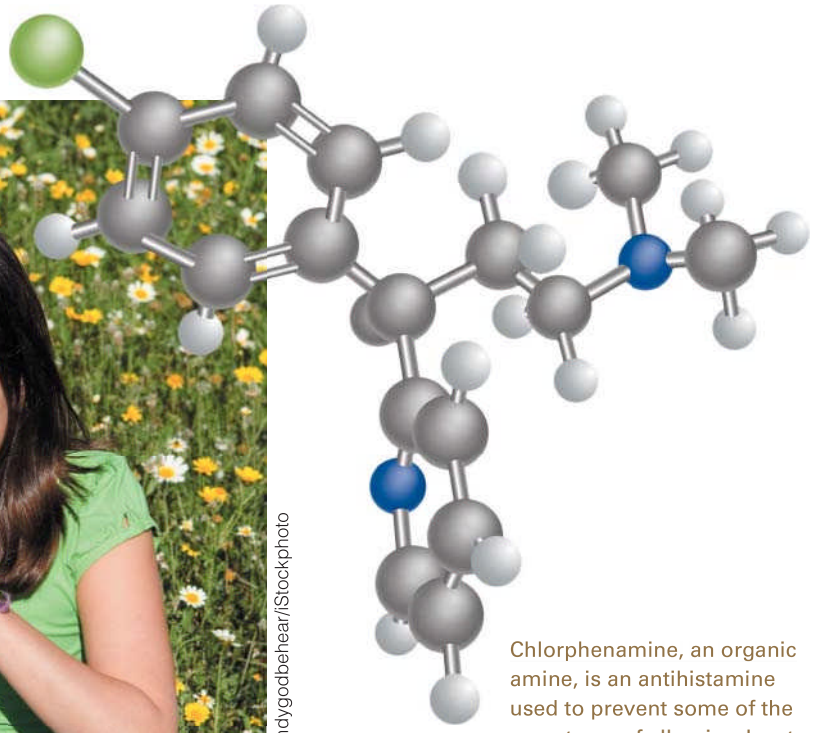
9.57 Pretend that you are back in the day of Faraday and do not know the structure of benzene. Propose possible alternative structural formulas for compounds with the molecular formula C_6H_6. As you think about alternative constitutional isomers with the molecular formula C_6H_6, keep in mind that in order for a six-carbon compound to only possess six hydrogens, it must have a number of rings, double bonds, or triple bonds. Be creative and try to use the following building blocks:

(a) Three-, four-, and five-membered rings.

(b) Carbon-carbon single, double, and triple bonds.

9.58 Propose a synthesis of 2,6-diisopropylphenol (Propofol) starting with phenol and any three-carbon reagents. Use the Internet to find the uses and cultural significance of Propofol.

© mandygodbehear/iStockphoto



Chlorphenamine, an organic amine, is an antihistamine used to prevent some of the symptoms of allergies. Inset: A model of chlorphenamine.

Amines

10

KEY QUESTIONS

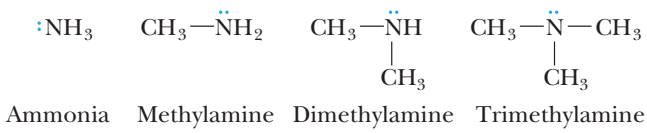
HOW TO

CHEMICAL CONNECTIONS

WE HAVE SEEN that carbon, hydrogen, and oxygen are common elements in many organic compounds. In the biological world, nitrogen is also widely encountered and ranks as the fourth most common element in organic compounds. DNA, proteins, and over 75% of pharmaceutical drugs on the market contain nitrogen, many in the form of the amine functional group. In this chapter, we learn about the properties and reactivity of amines, paying particular attention to their basicity and their nucleophilicity.

10.1 What Are Amines?

Amines are derivatives of ammonia (NH_3) in which one or more hydrogens are replaced by alkyl or aryl groups. Amines are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of hydrogen atoms of ammonia that are replaced by alkyl or aryl groups (Section 1.7B). As we saw with ammonia, the three atoms or groups bonded to the nitrogen in amines assume a trigonal pyramidal geometry:

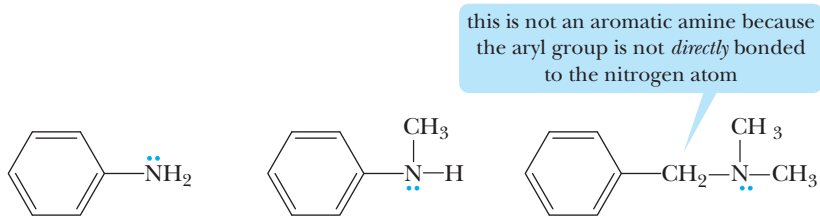


Ammonia	Methylamine (a 1° amine)	Dimethylamine (a 2° amine)	Trimethylamine (a 3° amine)

Aliphatic amine An amine in which nitrogen is bonded only to alkyl groups.

Aromatic amine An amine in which nitrogen is bonded to one or more aryl groups.

Amines are further divided into aliphatic amines and aromatic amines. In an **aliphatic amine**, all the carbons bonded directly to nitrogen are derived from alkyl groups; in an **aromatic amine**, one or more of the groups bonded directly to nitrogen are aryl groups:

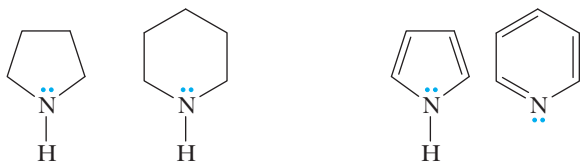


Aniline (a 1° aromatic amine) | *N*-Methylaniline (a 2° aromatic amine) | Benzyldimethylamine (a 3° aliphatic amine)

Heterocyclic amine An amine in which nitrogen is one of the atoms of a ring.

Heterocyclic aromatic amine An amine in which nitrogen is one of the atoms of an aromatic ring.

An amine in which the nitrogen atom is part of a ring is classified as a **heterocyclic amine**. When the nitrogen is part of an aromatic ring (Section 9.2), the amine is classified as a **heterocyclic aromatic amine**. Following are structural formulas for two heterocyclic aliphatic amines and two heterocyclic aromatic amines:

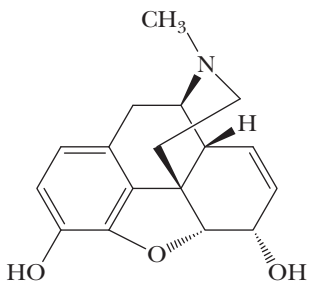


Pyrrolidine Piperidine (heterocyclic aliphatic amines) | Pyrrole Pyridine (heterocyclic aromatic amines)

Chemical Connections 10A

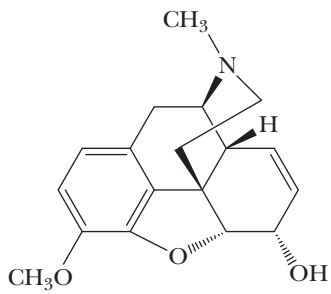
MORPHINE AS A CLUE IN THE DESIGN AND DISCOVERY OF DRUGS

The analgesic, soporific, and euphoriant properties of the dried juice obtained from unripe seed pods of the opium poppy *Papaver somniferum* have been known for centuries. By the beginning of the nineteenth century, the active principal, morphine, had been isolated and its structure determined:



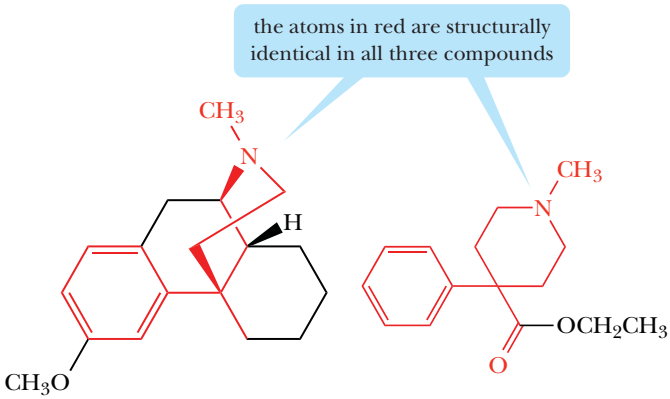
Morphine

Also occurring in the opium poppy is codeine, a monomethyl ether of morphine:



Codeine

Even though morphine is one of modern medicine's most effective painkillers, it has two serious side effects: It is addictive, and it depresses the respiratory control center of the central nervous system. Large doses of morphine can lead to death by respiratory failure. One strategy in the ongoing research to produce painkillers has been to synthesize compounds related in structure to morphine, in the hope that they would be equally effective analgesics, but with diminished side effects. Following are structural formulas for three such compounds that have proven to be clinically useful:



(–)-enantiomer = Levomethorphan
(+)-enantiomer = Dextromethorphan

Meperidine
(Demerol)

Levomethorphan is a potent analgesic. Interestingly, its dextrorotatory enantiomer, dextromethorphan, has no analgesic activity. It does, however, show approximately the same cough-suppressing activity as morphine and is used extensively in cough remedies.

It has been discovered that there can be even further simplification in the structure of morphine-like analgesics. One such simplification is represented by meperidine, the hydrochloride salt of which is the widely used analgesic Demerol®.

It was hoped that meperidine and related synthetic drugs would be free of many of the morphine-like undesirable side effects. It is now clear, however, that they are not. Meperidine, for example, is definitely addictive. In spite of much determined research, there are as yet no agents as effective as morphine for the relief of severe pain that are absolutely free of the risk of addiction.

How and in what regions of the brain does morphine act? In 1979, scientists discovered that there are specific receptor sites for morphine and other opiates and that these sites are clustered in the brain's limbic system, the area involved in emotion and the perception of pain. Scientists then asked, "Why does the human brain have receptor sites specific for morphine?" Could it be that the brain produces its own opiates? In 1974, scientists discovered that opiate-like compounds are indeed present in the brain; in 1975, they isolated a brain opiate that was named *enkephalin*, meaning "in the brain." Unlike morphine and its derivatives, enkephalin possesses an entirely different structure consisting of a sequence of five amino acids (Section 18.4). Scientists have yet to understand the role of these natural brain opiates. Perhaps when we do understand their biochemistry, we may discover clues that will lead to the design and synthesis of more potent, but less addictive, analgesics.

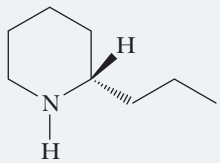
Question

Identify the functional groups in morphine and meperidine. Classify the amino group in these opiates as primary, secondary, or tertiary (Section 1.8).

EXAMPLE 10.1

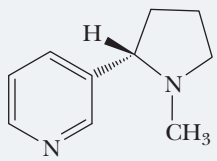
Alkaloids are basic nitrogen-containing compounds of plant origin, many of which have physiological activity when administered to humans. The ingestion of coniine, present in water hemlock, can cause weakness, labored respiration, paralysis, and, eventually, death. Coniine was the toxic substance in "poison hemlock" that caused the death of Socrates. In small doses, nicotine is an addictive stimulant. In larger doses, it causes depression, nausea, and vomiting. In still larger doses, it is a deadly poison. Solutions of nicotine in water are used as insecticides. Cocaine is a central nervous system stimulant obtained from the leaves of the coca plant. Classify each amino group in these alkaloids according to type (that is, primary, secondary, tertiary, heterocyclic, aliphatic, or aromatic):

(a)



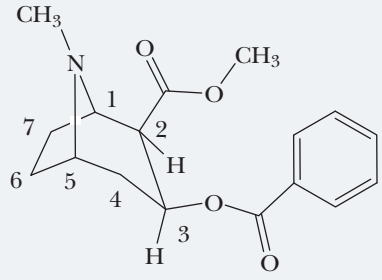
(*S*)-Coniine

(b)



(*S*)-Nicotine

(c)



Cocaine

STRATEGY

Locate each nitrogen in each compound. If a nitrogen is part of a ring, the amine is heterocyclic. If that ring is aromatic, it is classified as a heterocyclic aromatic amine (1°, 2°, or 3° does not apply). If the ring is not aromatic, it is a heterocyclic

aliphatic amine that should also be classified as 1°, 2°, or 3°. *Note*: The presence of more than one nitrogen can result in multiple classifications for the molecule, depending on the part of the compound being referred to.

SOLUTION

(a) A secondary (2°) heterocyclic aliphatic amine.
(b) One tertiary (3°) heterocyclic aliphatic amine and one heterocyclic aromatic amine.
(c) A tertiary (3°) heterocyclic aliphatic amine.

See problems 10.13–10.16

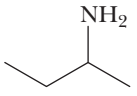
PROBLEM 10.1

Identify all carbon stereocenters in coniine, nicotine, and cocaine. Assign R/S configurations for all stereocenters in cocaine.

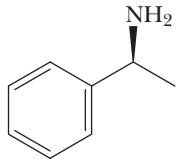
10.2 How Are Amines Named?

A. Systematic Names

Systematic names for aliphatic amines are derived just as they are for alcohols. The suffix *-e* of the parent alkane is dropped and is replaced by *-amine*; that is, they are named alkanamines:



2-Butanamine



(*S*)-1-Phenylethanamine

the number modifiers "di, tri, tetra, etc." are inserted based on the number of amino groups

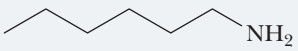
$H_2N(CH_2)_6NH_2$

1,6-Hexanediamine

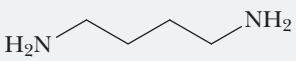
IUPAC nomenclature retains the common name **aniline** for $C_6H_5NH_2$, the simplest aromatic amine. Its simple derivatives are named with the prefixes *o-*, *m-*, and *p-*, or numbers to locate substituents. Several derivatives of aniline have common names that are still widely used.

EXAMPLE 10.2

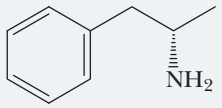
Write the IUPAC name or provide the structural formula for each amine:

(a) 

(b) 2-Methyl-1-propanamine

(c) 

(d) *trans*-4-Methylcyclohexanamine

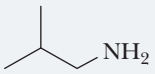
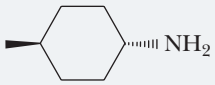
(e) 

STRATEGY

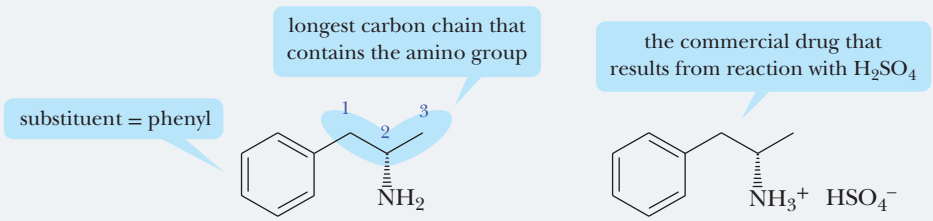
When naming, look for the longest chain of carbons that contains the amino group. This will allow you to determine the root name. Then identify and name the substituents, the atoms or groups of atoms that are not part of that chain of carbons.

To translate a name to a structure, identify the carbon chain from the root name and add the substituents to the correct position on the chain.

SOLUTION

(a) 1-Hexanamine **(b)**  **(c)** 1,4-Butanediamine **(d)** 

(e) The systematic name of this compound is (*S*)-1-phenyl-2-propanamine. Its common name is amphetamine. The dextrorotatory isomer of amphetamine (shown here) is a central nervous system stimulant and is manufactured and sold under several trade names. The salt with sulfuric acid is marketed as Dexedrine sulfate.



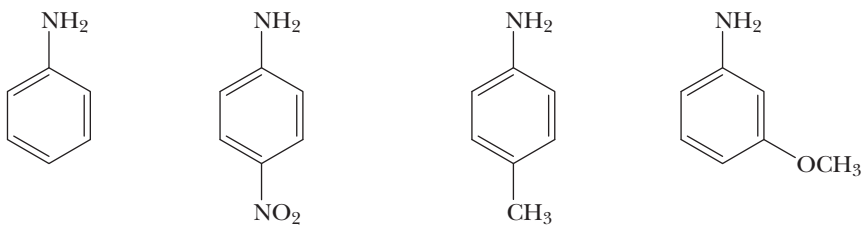
See problems 10.11, 10.12, 10.16

PROBLEM 10.2

Write a structural formula for each amine:

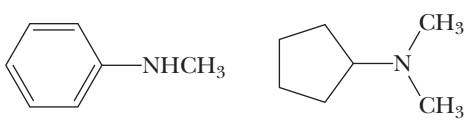
(a) 2-Methyl-1-propanamine **(b)** Cyclohexanamine **(c)** (*R*)-2-Butanamine **(d)** (2*S*,4*S*)-2,4-hexanediamine

Among these are **toluidine**, for a methyl-substituted aniline, and **anisidine**, for a methoxy-substituted aniline:



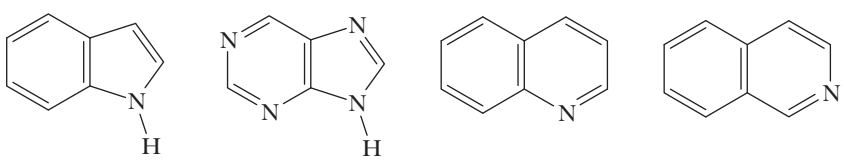
Aniline | 4-Nitroaniline (*p*-Nitroaniline) | 4-Methylaniline (*p*-Toluidine) | 3-Methoxyaniline (*m*-Anisidine)

Secondary and tertiary amines are commonly named as *N*-substituted primary amines. For unsymmetrical amines, the largest group is taken as the parent amine; then the smaller group or groups bonded to nitrogen are named, and their location is indicated by the prefix *N*- (indicating that they are bonded to nitrogen):



N-Methylaniline | *N*,*N*-Dimethylcyclopentanamine

Following are names and structural formulas for four heterocyclic aromatic amines, the common names of which have been retained by the IUPAC:

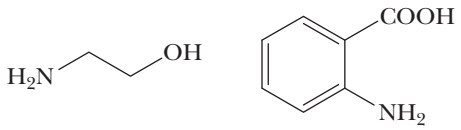


Indole | Purine | Quinoline | Isoquinoline

© Foodcollection.com/Alamy Stock Photo

Jasmine oil, which is used in perfumes and as a health supplement, contains 2.5% indole.

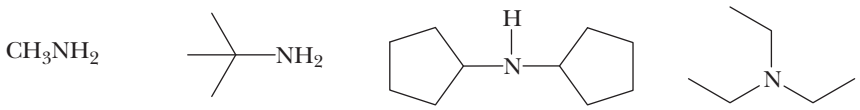
Among the various functional groups discussed in this text, the —NH_2 group has one of the lowest priorities. The following compounds each contain a functional group of higher precedence than the amino group, and, accordingly, the amino group is indicated by the prefix *amino-*:



2-Aminoethanol 2-Aminobenzoic acid

B. Common Names

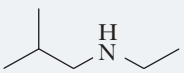
Common names for most aliphatic amines are derived by listing the alkyl groups bonded to nitrogen in alphabetical order in one word ending in the suffix *-amine*; that is, they are named as **alkylamines**:

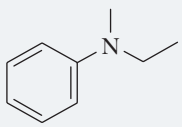


Methylamine *tert*-Butylamine Dicyclopentylamine Triethylamine

EXAMPLE 10.3

Write the IUPAC name or provide the structural formula for each amine:

(a) 

(b) Cyclohexylmethylamine **(c)** 

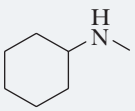
(d) Benzylamine

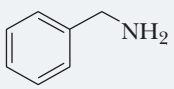
STRATEGY

When naming, look for the longest chain of carbons that contains the amino group. This will allow you to determine the root name. If the longest chain of carbons is a benzene ring, the amine may be named as an aniline derivative. When identifying the substituents, remember that substitutents bonded to a nitrogen are preceded by "*N*-."

To translate a name to a structure, identify the carbon chain from the root name and add the substituents to the correct position on the molecule.

SOLUTION

(a) *N*-ethyl-2-methyl-1-propanamine **(b)** 

(c) *N*-ethyl-*N*-methylaniline **(d)** 

See problems 10.11, 10.12, 10.16

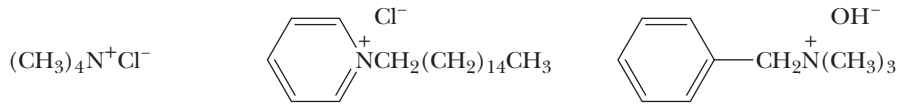
PROBLEM 10.3

Write a structural formula for each amine:

(a) Isobutylamine **(b)** Triphenylamine **(c)** Diisopropylamine **(d)** Butylcyclohexylamine

When four atoms or groups of atoms are bonded to a nitrogen atom, we name the compound as a salt of the corresponding amine. We replace the ending *-amine* (or aniline, pyridine, or the like) by *-ammonium* (or *anilinium*, *pyridinium*, or the like) and add the name of the anion (chloride, acetate, and so on). Compounds containing such ions have properties characteristic of salts, such as increased water solubility, high melting points, and

high boiling points. Following are three examples (cetylpyridinium chloride is used as a topical antiseptic and disinfectant):



Tetramethylammonium chloride | Hexadecylpyridinium chloride (Cetylpyridinium chloride) | Benzyltrimethylammonium hydroxide

Charles D. Winters

Several over-the-counter mouthwashes contain *N*-alkylatedpyridinium chlorides as an antibacterial agent.

10.3 What Are the Characteristic Physical Properties of Amines?

Amines are polar compounds, and both primary and secondary amines form intermolecular hydrogen bonds (Figure 10.1).

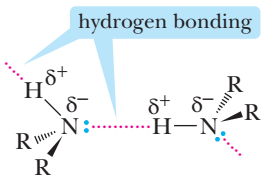


FIGURE 10.1 Intermolecular association of 1° and 2° amines by hydrogen bonding. Nitrogen is approximately tetrahedral in shape, with the axis of the hydrogen bond along the fourth position of the tetrahedron.

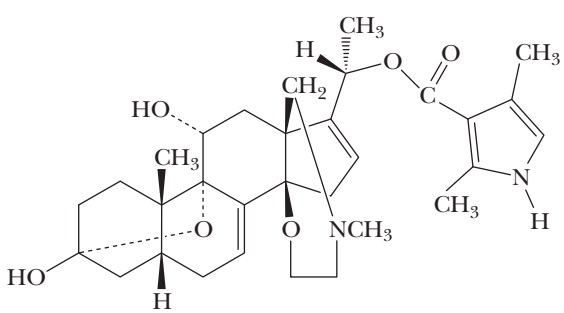
Chemical Connections 10B

THE POISON DART FROGS OF SOUTH AMERICA: LETHAL AMINES

The Noanamá and Embrá peoples of the jungles of western Colombia have used poison blow darts for centuries, perhaps millennia. The poisons are obtained from the skin secretions of several highly colored frogs of the genus *Phyllobates* (*neará* and *kokoi* in the language of the native peoples). A single frog contains enough poison for up to 20 darts. For the most poisonous species (*Phyllobates terribilis*), just rubbing a dart over the frog's back suffices to charge the dart with poison.

Scientists at the National Institutes of Health became interested in studying these poisons when it was discovered that they act on cellular ion channels, which would make them useful tools in basic research on mechanisms of ion transport. A field station was established in western Colombia to collect the relatively common poison dart frogs. From 5,000 frogs, 11 mg of batrachotoxin and batrachotoxinin A were isolated. These names are derived from *batrachos*, the Greek word for frog.

Batrachotoxin and batrachotoxinin A are among the most lethal poisons ever discovered:



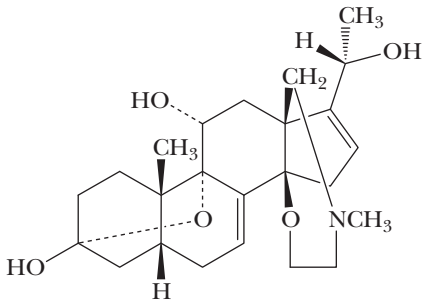
Batrachotoxin

© Alfredo Maiquez/iStockphoto

Poison dart frog, *Phyllobates terribilis*.

It is estimated that as little as 200 μg of batrachotoxin is sufficient to induce irreversible cardiac arrest in a human being. It has been determined that they act by causing voltage-gated Na^+ channels in nerve and muscle cells to be blocked in the open position, which leads to a huge influx of Na^+ ions into the affected cell.

The batrachotoxin story illustrates several common themes in the discovery of new drugs. First, information about the kinds of biologically active compounds and their sources are often obtained from the native peoples of a region. Second, tropical rain forests are a rich source of structurally complex, biologically active substances. Third, an entire ecosystem, not only the plants, is a potential source of fascinating organic molecules.



Batrachotoxinin A

Question

Would you expect batrachotoxin or batrachotoxinin A to be more soluble in water? Why?

Predict the product formed from the reaction of batrachotoxin with one equivalent of a weak acid such as acetic acid, CH_3COOH.

An N—H⋯⋯N hydrogen bond is weaker than an O—H⋯⋯O hydrogen bond, because the difference in electronegativity between nitrogen and hydrogen (3.0 − 2.1 = 0.9) is less than that between oxygen and hydrogen (3.5 − 2.1 = 1.4). We can illustrate the effect of intermolecular hydrogen bonding by comparing the boiling points of methylamine and methanol:

	CH_3NH_2	CH_3OH
molecular weight (g/mol)	31.1	32.0
boiling point (°C)	−6.3	65.0

Both compounds have polar molecules and interact in the pure liquid by hydrogen bonding. Methanol has the higher boiling point because hydrogen bonding between its molecules is stronger than that between molecules of methylamine.

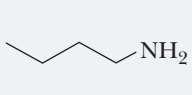
All classes of amines form hydrogen bonds with water and are more soluble in water than are hydrocarbons of comparable molecular weight. Most low-molecular-weight amines are completely soluble in water (Table 10.1). Higher-molecular-weight amines are only moderately soluble or insoluble.

TABLE 10.1 Physical Properties of Selected Amines

Name	Structural Formula	Melting Point (°C)	Boiling Point (°C)	Solubility in Water
Ammonia	NH_3	−78	−33	very soluble
Primary Amines				
methylamine	CH_3NH_2	−95	−6	very soluble
ethylamine	$CH_3CH_2NH_2$	−81	17	very soluble
propylamine	$CH_3CH_2CH_2NH_2$	−83	48	very soluble
butylamine	$CH_3(CH_2)_3NH_2$	−49	78	very soluble
benzylamine	$C_6H_5CH_2NH_2$	10	185	very soluble
cyclohexylamine	$C_6H_{11}NH_2$	−17	135	slightly soluble
Secondary Amines				
dimethylamine	$(CH_3)_2NH$	−93	7	very soluble
diethylamine	$(CH_3CH_2)_2NH$	−48	56	very soluble
Tertiary Amines				
trimethylamine	$(CH_3)_3N$	−117	3	very soluble
triethylamine	$(CH_3CH_2)_3N$	−114	89	slightly soluble
Aromatic Amines				
aniline	$C_6H_5NH_2$	−6	184	slightly soluble
Heterocyclic Aromatic Amines				
pyridine	C_5H_5N	−42	116	very soluble

EXAMPLE 10.4

Account for the fact that butylamine has a higher boiling point than *t*-butylamine.



Butylamine
bp 78 °C

t-Butylamine
bp 46 °C

STRATEGY

Identify structural differences that might affect the intermolecular attractions between the molecules of each compound.

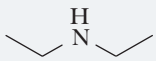
SOLUTION

Both molecules can participate in hydrogen bonding. However, the *t*-butyl group is larger and bulkier, making it more difficult for the molecules of *t*-butylamine to hydrogen bond to each other.

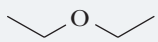
See problems 10.18–10.20

PROBLEM 10.4

Account for the fact that diethylamine has a higher boiling point than diethyl ether.



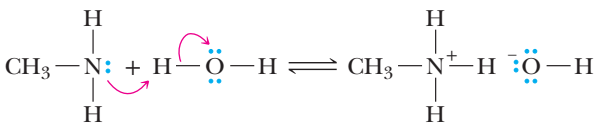
Diethylamine
bp 55 °C



Diethyl ether
bp 34.6 °C

10.4 What Are the Acid–Base Properties of Amines?

Like ammonia, all amines are weak bases, and aqueous solutions of amines are basic. The following acid–base reaction between an amine and water is written using curved arrows to emphasize that, in this proton-transfer reaction, the unshared pair of electrons on nitrogen forms a new covalent bond with hydrogen and displaces hydroxide ion:



Methylamine

Methylammonium hydroxide

The equilibrium constant for the reaction of an amine with water, K_{eq}, has the following form, illustrated for the reaction of methylamine with water to give methylammonium hydroxide:

$$K_{eq} = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2][H_2O]}$$

Because the concentration of water in dilute solutions of methylamine in water is essentially a constant ($[H_2O] = 55.5$ mol/L), it is combined with K_{eq} in a new constant called a *base ionization constant*, K_b. The value of K_b for methylamine is 4.37×10^{-4} ($pK_b = 3.36$):

$$K_b = K_{eq}[H_2O] = \frac{[CH_3NH_3^+][OH^-]}{[CH_3NH_2]} = 4.37 \times 10^{-4} \quad pK_b = 3.36$$

It is also common to discuss the basicity of amines by referring to the acid ionization constant of the corresponding conjugate acid, as illustrated for the ionization of the methylammonium ion:

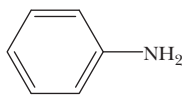
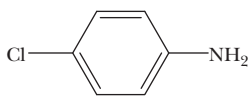
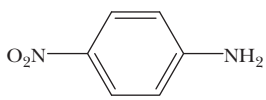
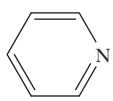
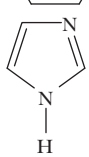
$$CH_3NH_3^+ + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+ \quad K_a = \frac{[CH_3NH_2][H_3O^+]}{[CH_3NH_3^+]} = 2.29 \times 10^{-11} \quad pK_a = 10.64$$

Values of pK_a and pK_b for any acid–conjugate base pair are related by the equation:

$$pK_a + pK_b = 14.00$$

Values of pK_a and pK_b for selected amines are given in Table 10.2.

TABLE 10.2 Base Strengths (pK_b) of Selected Amines and Acid Strengths (pK_a) of Their Conjugate Acids*

Amine	Structure	pK_b	pK_a
Ammonia	NH_3	4.74	9.26
Primary Amines			
methylamine	CH_3NH_2	3.36	10.64
ethylamine	$CH_3CH_2NH_2$	3.19	10.81
cyclohexylamine	$C_6H_{11}NH_2$	3.34	10.66
Secondary Amines			
dimethylamine	$(CH_3)_2NH$	3.27	10.73
diethylamine	$(CH_3CH_2)_2NH$	3.02	10.98
Tertiary Amines			
trimethylamine	$(CH_3)_3N$	4.19	9.81
triethylamine	$(CH_3CH_2)_3N$	3.25	10.75
Aromatic Amines			
aniline		9.37	4.63
4-methylaniline (*p*-toluidine)		8.92	5.08
4-chloroaniline		9.85	4.15
4-nitroaniline		13.0	1.0
Heterocyclic Aromatic Amines			
pyridine		8.75	5.25
imidazole		7.05	6.95

*For each amine, $pK_a + pK_b = 14.00$.

EXAMPLE 10.5

Predict the position of equilibrium for this acid–base reaction:

$$CH_3NH_2 + CH_3COOH \rightleftharpoons CH_3NH_3^+ + CH_3COO^-$$

STRATEGY

Use the approach we developed in Section 2.4 to predict the position of equilibrium in acid–base reactions. Equilibrium favors reaction of the stronger acid and stronger base to form the weaker acid and the weaker base. It is helpful to remember that even though ammonium ions are positively charged, they are much weaker acids than carboxylic acids.

SOLUTION

In this reaction, equilibrium favors the formation of methylammonium ion and acetate ion, which are the weaker acid and base, respectively:

$$CH_3NH_2 + CH_3COOH \rightleftharpoons CH_3NH_3^+ + CH_3COO^-$$

$pK_a = 4.76$ $pK_a = 10.64$

Stronger base — Stronger acid — Weaker acid — Weaker base

See problem 10.25

PROBLEM 10.5

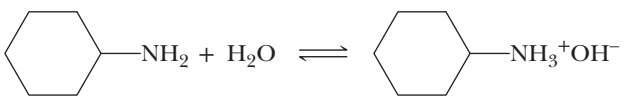
Predict the position of equilibrium for this acid–base reaction:

$$CH_3NH_3^+ + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+$$

Given information such as that in Table 10.2, we can make the following generalizations about the acid–base properties of the various classes of amines:

1. All aliphatic amines have about the same base strength, pK_b 3.0–4.0, and are slightly stronger bases than ammonia.

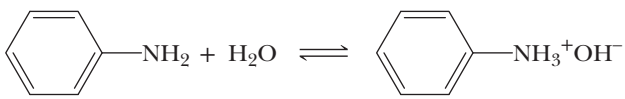
2. Aromatic amines and heterocyclic aromatic amines are considerably weaker bases than are aliphatic amines. Compare, for example, values of pK_b for cyclohexylamine and aniline:



Cyclohexylamine — Cyclohexylammonium hydroxide

$pK_b = 3.34$
$K_b = 4.5 \times 10^{-4}$

the lower the value of pK_b, the stronger the base

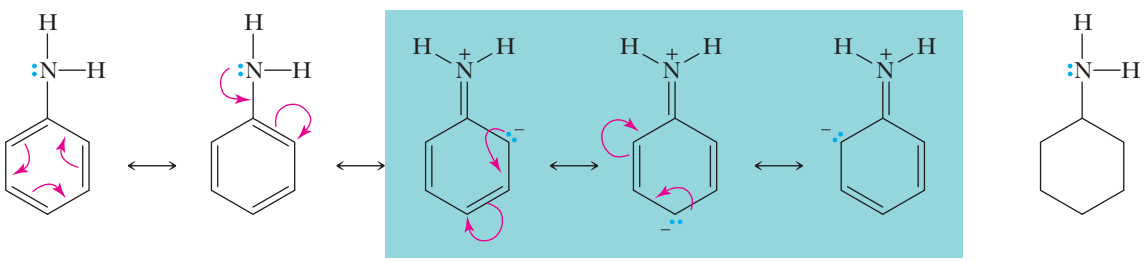


Aniline — Anilinium hydroxide

$pK_b = 9.37$
$K_b = 4.3 \times 10^{-10}$

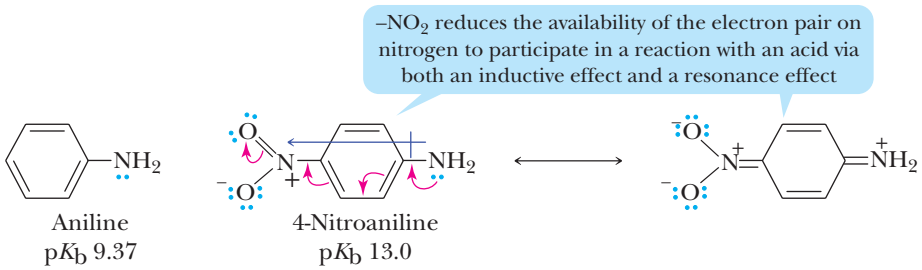
The base ionization constant for aniline is smaller (the larger the value of pK_b, the weaker is the base) than that for cyclohexylamine by a factor of 10^6.

Aromatic amines are weaker bases than are aliphatic amines because of the resonance interaction of the unshared pair on nitrogen with the pi system of the aromatic ring. Because no such resonance interaction is possible for an alkylamine, the electron pair on its nitrogen is more available for reaction with an acid:



Two Kekulé structures — Interaction of the electron pair on nitrogen with the pi system of the aromatic ring reduces the availability of the electron pair to participate in a reaction with an acid — No resonance is possible with alkylamines

3. Electron-withdrawing groups such as halogen, nitro, and carbonyl decrease the basicity of substituted aromatic amines by decreasing the availability of the electron pair on nitrogen:

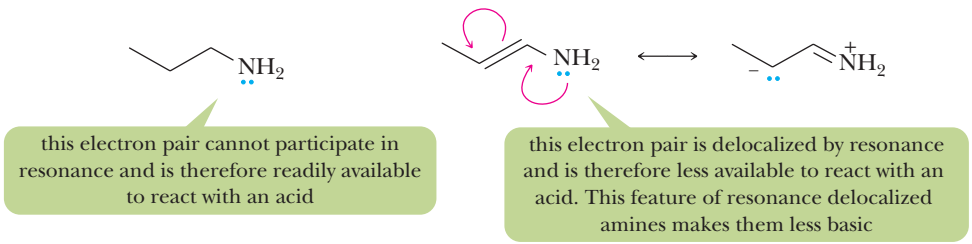


Recall from Section 9.8B that these same substituents increase the acidity of phenols.

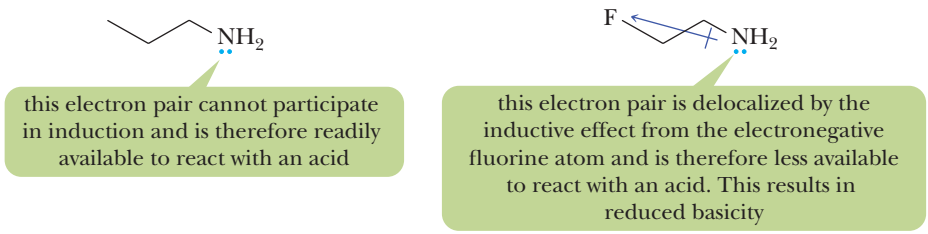
HOW TO 10.1 Predict the Relative Basicity of Amines

The basicity of an amine depends on the ability of its nitrogen atom to donate its lone pair of electrons in an acid–base reaction. When assessing an electron pair's availability, look for the following possibilities:

(a) Resonance contribution



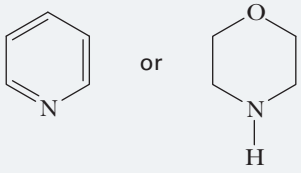
(b) Induction



EXAMPLE 10.6

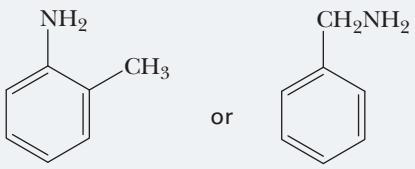
Select the stronger base in each pair of amines:

(a)



(A) (B)

(b)



(C) (D)

STRATEGY

Use Table 10.2 to compare values of pK_b. Alternatively, look for resonance, inductive, or steric effects that might enhance or diminish the availability of a lone pair on the nitrogen of each molecule.

SOLUTION

(a) Morpholine (B) is the stronger base (pK_b 5.79). It has a basicity comparable to that of secondary aliphatic amines. Pyridine (A), a heterocyclic aromatic amine (pK_b 8.75), is considerably less basic than aliphatic amines.

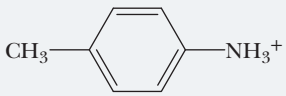
(b) Benzylamine (D), a primary aliphatic amine, is the stronger base (pK_b 3–4). *o*-Toluidine (C), an aromatic

amine, is the weaker base (pK_b 9–10). In the absence of Table 10.2, one can see that the electron pair on nitrogen in *o*-toluidine can participate in resonance with the benzene ring, while there are no resonance possibilities in benzylamine. This results in *o*-toluidine's electron pair being less available for reaction with an acid.

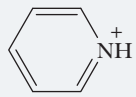
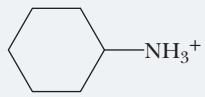
See problems 10.21–10.25, 10.29–10.31

PROBLEM 10.6

Select the stronger acid from each pair of ions:

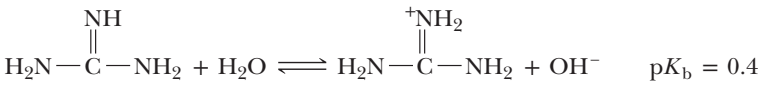
(a)  or 

(A) (B)

(b)  or 

(C) (D)

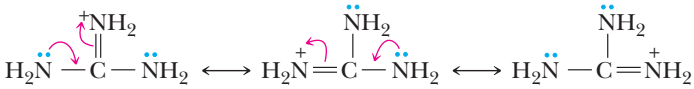
Guanidine (pK_b 0.4) is the strongest base among neutral compounds:



pK_b = 0.4

Guanidine Guanidinium ion

The remarkable basicity of guanidine is attributed to the fact that the positive charge on the guanidinium ion is delocalized equally over the three nitrogen atoms, as shown by these three equivalent contributing structures:

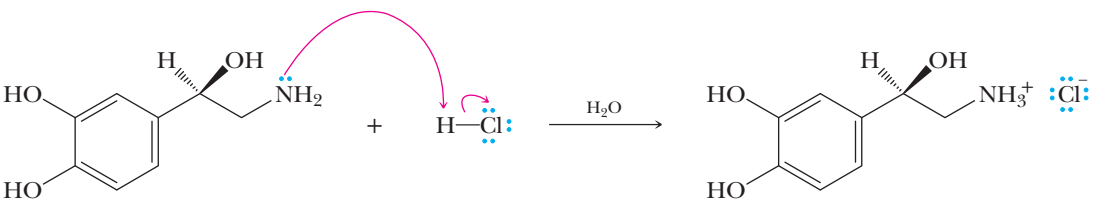


Three equivalent contributing structures

Hence, the guanidinium ion is a highly stable cation. The presence of a guanidine group on the side chain of the amino acid arginine accounts for the basicity of its side chain (Section 18.2A).

10.5 What Are the Reactions of Amines with Acids?

Amines, whether soluble or insoluble in water, react quantitatively with strong acids to form water-soluble salts, as illustrated by the reaction of (*R*)-norepinephrine (noradrenaline) with aqueous HCl to form a hydrochloride salt:



(*R*)-Norepinephrine (only slightly soluble in water)

(*R*)-Norepinephrine hydrochloride (a water-soluble salt)

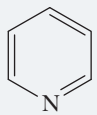
Norepinephrine, secreted by the medulla of the adrenal gland, is a neurotransmitter. It has been suggested that it is a neurotransmitter in those areas of the brain that mediate emotional behavior.

The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds. Shown in Figure 10.2 is a flowchart for the separation of aniline from anisole. Note that aniline is recovered from its salt by treatment with NaOH.

EXAMPLE 10.7

Complete each acid–base reaction, and name the salt formed:

(a) $(CH_3CH_2)_2NH + HCl \longrightarrow$

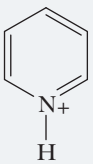
(b)  $+ CH_3COOH \longrightarrow$

STRATEGY

Identify the acidic proton in the acid. The amine nitrogen will abstract this proton to form the ammonium salt. In naming an ammonium salt, replace the ending *-amine* (or aniline, pyridine, or the like) by *-ammonium* (or *anilinium, pyridinium,* or the like) and add the name of the anion (chloride, acetate, and so on).

SOLUTION

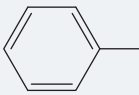
(a) $(CH_3CH_2)_2NH_2^+Cl^-$
Diethylammonium chloride

(b)  CH_3COO^-
Pyridinium acetate

See problems 10.25, 10.29, 10.31, 10.32, 10.35

PROBLEM 10.7

Complete each acid–base reaction and name the salt formed:

(a) $(CH_3CH_2)_3N + HCl \longrightarrow$ **(b)**  $+ CH_3COOH \longrightarrow$ **(c)**  $+ H_2SO_4 \longrightarrow$

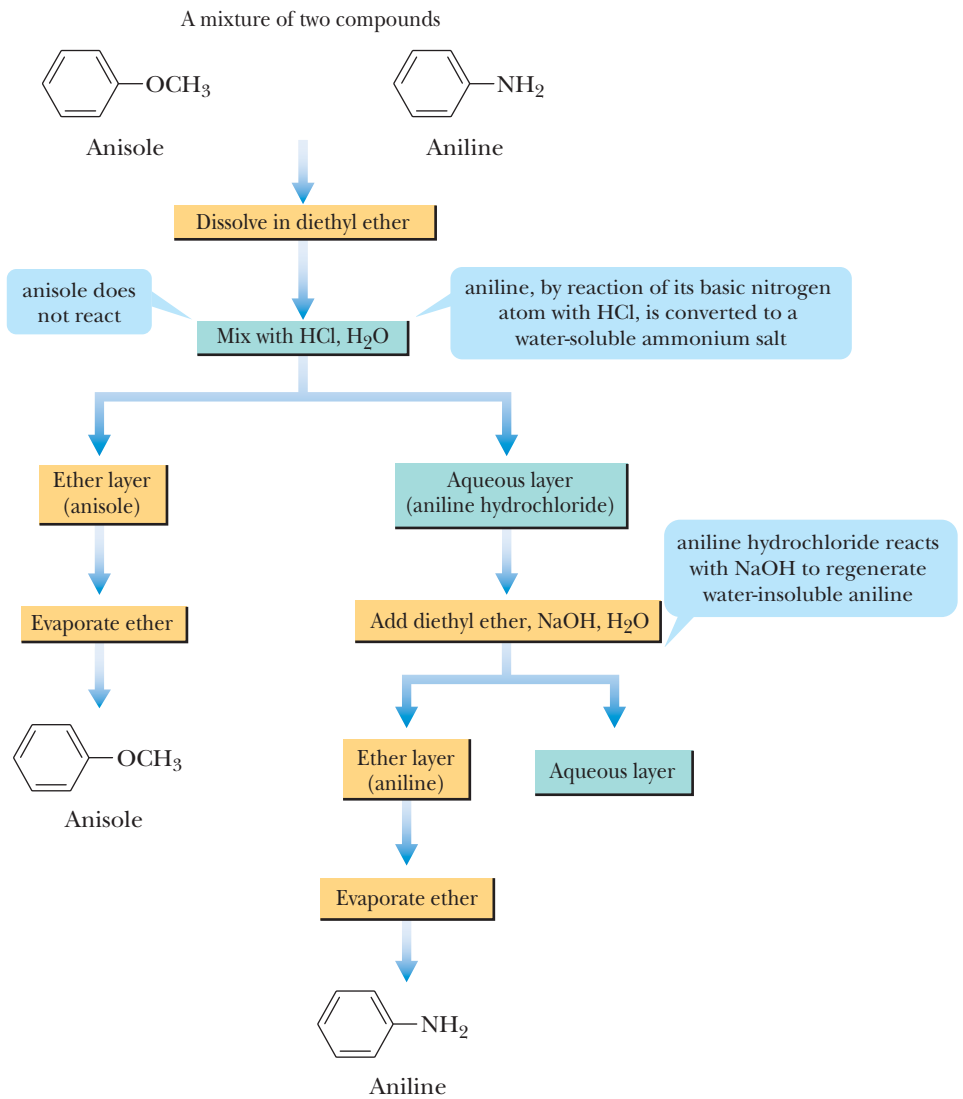
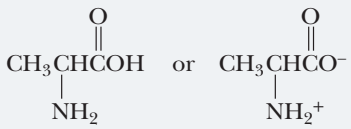


FIGURE 10.2 Separation and purification of an amine and a neutral compound.

EXAMPLE 10.8

Following are two structural formulas for alanine (2-aminopropanoic acid), one of the building blocks of proteins (Chapter 18):



(A) (B)

Is alanine better represented by structural formula (A) or structural formula (B)?

STRATEGY

Begin by considering the acidity and basicity of the functional groups within alanine. How might they react if they were part of separate molecules?

SOLUTION

Structural formula (A) contains both an amino group (a base) and a carboxyl group (an acid). Proton transfer from the stronger acid (—COOH) to the stronger base ($—NH_2$) gives an internal salt; therefore, (B) is the better representation for alanine. Within the field of amino acid chemistry, the internal salt represented by (B) is called a **zwitterion** (Chapter 18).

PROBLEM 10.8

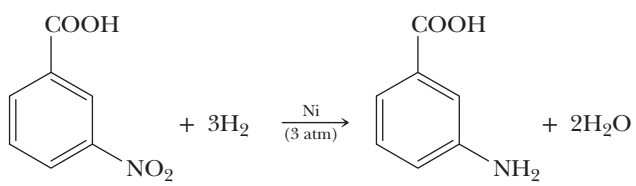
As shown in Example 10.8, alanine is better represented as an internal salt. Suppose that the internal salt is dissolved in water.

(a) In what way would you expect the structure of alanine in aqueous solution to change if concentrated HCl were added to adjust the pH of the solution to 2.0?

(b) In what way would you expect the structure of alanine in aqueous solution to change if concentrated NaOH were added to bring the pH of the solution to 12.0?

10.6 How Are Arylamines Synthesized?

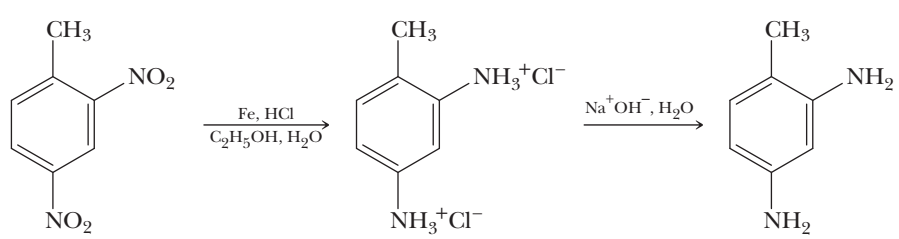
As we have already seen (Section 9.6B), the nitration of an aromatic ring introduces a $—NO_2$ group. A particular value of nitration is the fact that the resulting nitro group can be reduced to a primary amino group, $—NH_2$, by hydrogenation in the presence of a transition metal catalyst such as nickel, palladium, or platinum:



3-Nitrobenzoic acid 3-Aminobenzoic acid

This method has the potential disadvantage that other susceptible groups, such as a carbon–carbon double bond, and the carbonyl group of an aldehyde or ketone, may also be reduced. Note that neither the —COOH nor the aromatic ring is reduced under these conditions.

Alternatively, a nitro group can be reduced to a primary amino group by a metal in acid:

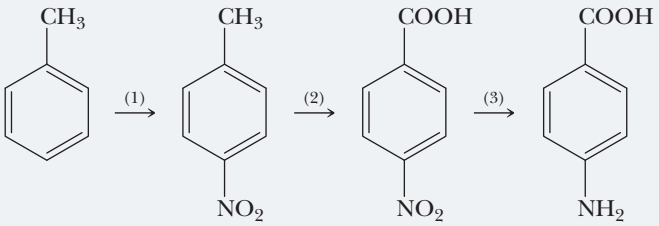


2,4-Dinitrotoluene 2,4-Diaminotoluene

The most commonly used metal-reducing agents are iron, zinc, and tin in dilute HCl. When reduced by this method, the amine is obtained as a salt, which is then treated with a strong base to liberate the free amine.

EXAMPLE 10.9

Show the reagents that will bring about each step in this conversion of toluene to 4-aminobenzoic acid:



Toluene

4-Amino-benzoic acid

STRATEGY

Use a combination of reactions from this chapter and previous chapters. Remember to consider the regioselectivity of reactions.

SOLUTION

STEP 1: Nitration of toluene, using nitric acid/sulfuric acid (Section 9.6B), followed by separation of the ortho and para isomers.

STEP 2: Oxidation of the benzylic carbon, using chromic acid (Section 9.4).

STEP 3: Reduction of the nitro group, either using H_2 in the presence of a transition metal catalyst or using Fe, Sn, or Zn in the presence of aqueous HCl (Section 10.6).

See problems 10.36–10.44

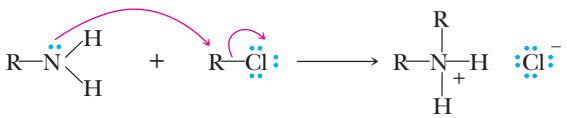
PROBLEM 10.9

Show how you can use the same set of steps in Example 10.9, but in a different order, to convert toluene to 3-aminobenzoic acid.

10.7 How Do Amines Act as Nucleophiles?

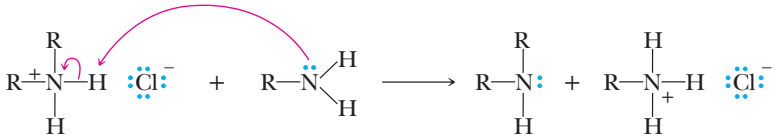
In Chapter 7, we learned that amines are moderate nucleophiles (Table 7.2) due to the presence of a lone pair of electrons on the nitrogen atom. Therefore, they should undergo nucleophilic substitution reactions with haloalkanes and other compounds containing a good leaving group (Section 7.5).

Step 1: Reaction of an electrophile and a nucleophile to form a new covalent bond. The nitrogen atom of an amine displaces chlorine in a haloalkane to yield an ammonium salt.



(a nucleophile) (an electrophile)

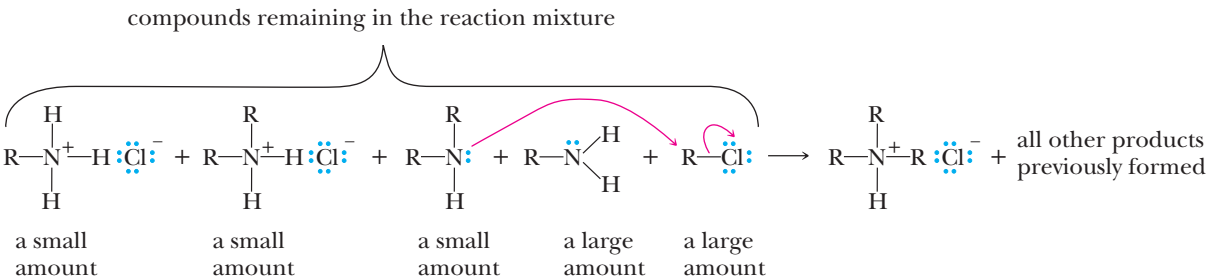
Step 2: Take a proton away. At the beginning of this reaction, when only a few product molecules are formed, plenty of amine starting material (a weak base) remains to react with the hydrogen of the ammonium salt to yield a secondary amine and another ammonium salt.



unreacted starting material

Remaining in the reaction mixture are some initial product, $R_2NH_2^+\ Cl^-$, some of the secondary amine, R_2NH, and lots of unreacted starting material and haloalkane.

Step 3: Reaction of an electrophile and a nucleophile to form a new covalent bond. The secondary amine is also a nucleophile, and because only a few of the initial R—Cl molecules have reacted at this early stage of the reaction, there are plenty left to react with either amine now in the reaction mixture.



The process can continue to give one other nitrogen-based product, the quaternary ammonium salt. The final composition of the reaction will consist of varying ratios of RNH_2, R_2NH, R_3N, and $R_4N^+Cl^-$. Because the ratio of products is difficult to control or predict, we avoid using an amine (or ammonia) as a nucleophile in nucleophilic aliphatic substitution reactions.

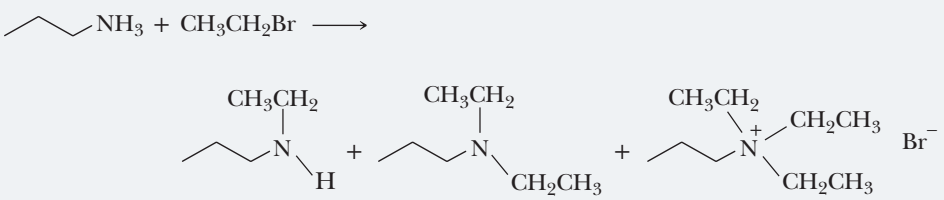
EXAMPLE 10.10

Determine all possible nitrogen-based products that can be formed in the following reaction:

STRATEGY

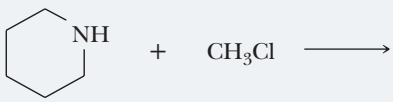
Keep in mind that the reaction of amines with haloalkanes often results in multiple nitrogen-based products with one or more alkyl groups from the haloalkane forming a bond with the nitrogen atom of the original amine.

SOLUTION



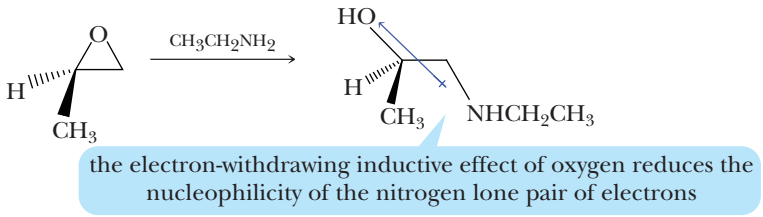
PROBLEM 10.10

Determine all possible nitrogen-based products that can be formed in the following reaction:



Although the use of amines in nucleophilic aliphatic substitution is problematic due to the mixtures of products that result, recall from Section 8.4C that amines are excellent nucleophiles for ring opening reactions of epoxides. This is because the inductive effect of

the hydroxyl oxygen atom diminishes the nucleophilicity of the nitrogen atom in the product:



SUMMARY OF KEY QUESTIONS

10.1 What Are Amines?

- Amines are derivatives of ammonia (NH_3) in which one or more hydrogens are replaced by alkyl or aryl groups.
- Amines are classified as **primary**, **secondary**, or **tertiary**, depending on the number of hydrogen atoms of ammonia replaced by alkyl or aryl groups.
- In an **aliphatic amine**, all carbon atoms bonded to nitrogen are derived from alkyl groups.
- In an **aromatic amine**, one or more of the groups bonded to nitrogen are aryl groups.
- A **heterocyclic amine** is an amine in which the nitrogen atom is part of a ring.
- A **heterocyclic aromatic amine** is an amine in which the nitrogen atom is part of an aromatic ring.

10.2 How Are Amines Named?

- In systematic nomenclature, aliphatic amines are named **alkanamines**.
- In the common system of nomenclature, aliphatic amines are named **alkylamines**; the alkyl groups are listed in alphabetical order in one word ending in the suffix *-amine*.
- An ion containing nitrogen bonded to four alkyl or aryl groups is named as a **quaternary ammonium ion**.

10.3 What Are the Characteristic Physical Properties of Amines?

- Amines are polar compounds, and primary and secondary amines associate by intermolecular hydrogen bonding.
- Because an N—H–––N hydrogen bond is weaker than an O—H–––O hydrogen bond, amines have lower boiling points than alcohols of comparable molecular weight and structure.
- All classes of amines form hydrogen bonds with water and are more soluble in water than are hydrocarbons of comparable molecular weight.

10.4 What Are the Acid–Base Properties of Amines?

- Amines are weak bases, and aqueous solutions of amines are basic. The **base ionization constant** for an amine in water is given the symbol K_b.
- It is also common to discuss the acid–base properties of amines by reference to the **acid ionization constant**, K_a, for the conjugate acid of the amine.
- Acid and base ionization constants for an amine in water are related by the equation $pK_a + pK_b = 14.0$.

10.5 What Are the Reactions of Amines with Acids?

- Amines react quantitatively with strong acids to form water-soluble salts.
- The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds.

10.6 How Are Arylamines Synthesized?

- Arylamines can be made by reducing the nitro group on a benzene ring.

10.7 How Do Amines Act as Nucleophiles?

- Amines are moderate nucleophiles and can participate in **nucleophilic aliphatic substitution** reactions.
- Reaction of ammonia or amines with haloalkanes often results in multiple products in varying ratios.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. An amine with an $—NH_2$ group bonded to a tertiary carbon is classified as a tertiary amine. (10.1)
2. The reaction of an amine with a haloalkane initially results in an ammonium halide salt. (10.7)
3. An efficient way to make diethylamine is to react ammonia with two equivalents of chloroethane. (10.7)
4. The IUPAC name of $CH_3CH_2CH_2CH_2NHCH_3$ is 2-pentanamine. (10.2)
5. An amino group can be directly added to a benzene ring via an electrophilic aromatic substitution reaction. (10.6)
6. A tertiary amine would be expected to be more water soluble than a secondary amine of the same molecular formula. (10.3)
7. The pK_b of an amine can be determined from the pK_a of its conjugate acid. (10.4)
8. The lower the value of pK_b, the stronger the base. (10.4)
9. The basicity of amines and the solubility of amine salts in water can be used to separate amines from water-insoluble, nonbasic compounds. (10.5)
10. Aromatic amines are more basic than aliphatic amines. (10.4)
11. A heterocyclic aromatic amine must contain one or more aryl groups directly bonded to nitrogen outside of the ring. (10.1)
12. Guanidine is a strong neutral base because its conjugate acid is resonance stabilized. (10.4)
13. Ammonia is a slightly weaker base than most aliphatic amines. (10.4)
14. An amino group forms stronger hydrogen bonds than a hydroxy group. (10.3)
15. A heterocyclic amine must contain a ring and a nitrogen atom as a member of the ring. (10.1)
16. An electron-withdrawing group in an amine decreases its basicity. (10.4)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

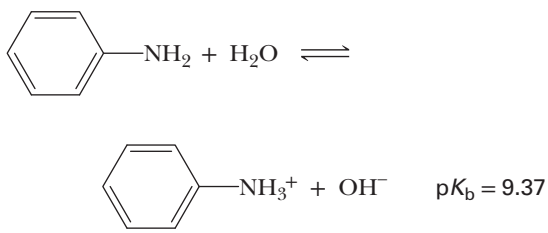
Answers: (1) F (2) T (3) F (4) F (5) F (6) F (7) T (8) T (9) T (10) F (11) F (12) T (13) T (14) F (15) T (16) T

KEY REACTIONS

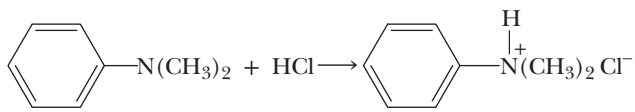
1. **Basicity of Aliphatic Amines (Section 10.4)**
   Most aliphatic amines have comparable basicities (pK_b 3.0–4.0) and are slightly stronger bases than ammonia:

$$CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^+ + OH^- \qquad pK_b = 3.36$$

2. **Basicity of Aromatic Amines (Section 10.4)**
   Aromatic amines (pK_b 9.0–10.0) are considerably weaker bases than are aliphatic amines. Resonance stabilization from interaction of the unshared electron pair on nitrogen with the pi system of the aromatic ring decreases the availability of that electron pair for reaction with an acid. Substitution on the ring by electron-withdrawing groups decreases the basicity of the $—NH_2$ group:

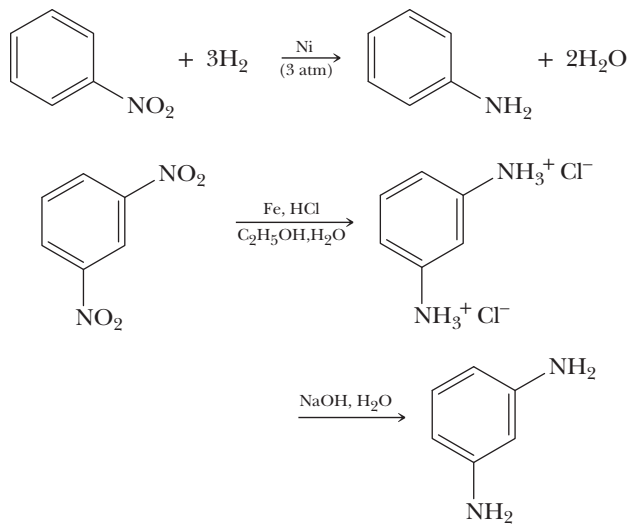


3. **Reaction of Amines with Strong Acids (Section 10.5)**
   All amines react quantitatively with strong acids to form water-soluble salts:



Insoluble in water — A water-soluble salt

4. **Reduction of an Aromatic $—NO_2$ Group (Section 10.6)**
   An $—NO_2$ group, for example on an aromatic ring, can be reduced to an amino group by catalytic hydrogenation or by treatment with a metal and hydrochloric acid, followed by a strong base to liberate the free amine:



PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

Structure and Nomenclature

10.11 Draw a structural formula for each amine: **(See Examples 10.2, 10.3)**

(a) (*R*)-2-Butanamine
(b) 1-Octanamine
(c) 2,2-Dimethyl-1-propanamine
(d) 1,5-Pentanediamine
(e) 2-Bromoaniline
(f) Tributylamine
(g) *N,N*-Dimethylaniline
(h) Benzylamine
(i) *tert*-Butylamine
(j) *N*-Ethylcyclohexanamine
(k) Diphenylamine
(l) Isobutylamine

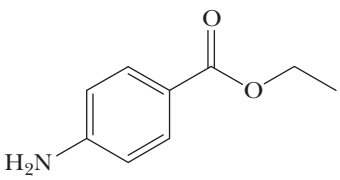
10.12 Draw a structural formula for each amine: **(See Examples 10.2, 10.3)**

(a) 4-Aminobutanoic acid
(b) 2-Aminoethanol (ethanolamine)
(c) 2-Aminobenzoic acid
(d) (*S*)-2-Aminopropanoic acid (alanine)
(e) 4-Aminobutanal
(f) 4-Amino-2-butanone

10.13 Draw examples of 1°, 2°, and 3° amines that contain at least four sp^3 hybridized carbon atoms. Using the same criterion, provide examples of 1°, 2°, and 3° alcohols. How does the classification system differ between the two functional groups? **(See Example 10.1)**

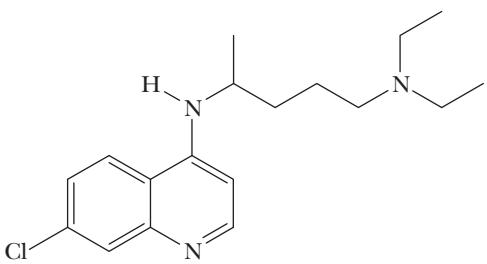
***10.14** Classify each amino group as primary, secondary, or tertiary and as aliphatic or aromatic: **(See Example 10.1)**

(a)



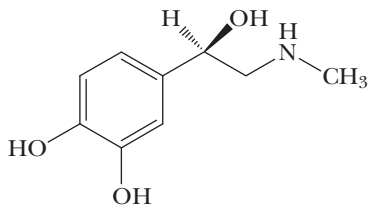
Benzocaine
(a topical anesthetic)

(b)

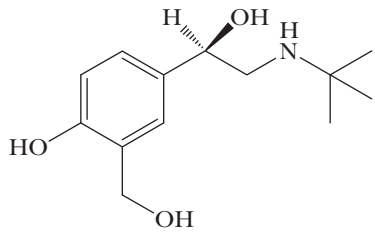


Chloroquine
(a drug for the treatment of malaria)

***10.15** Epinephrine is a hormone secreted by the adrenal medulla. Among epinephrine's actions, it is a bronchodilator. Albuterol, sold under several trade names, including Proventil® and Salbumol®, is one of the most effective and widely prescribed antiasthma drugs. The R enantiomer of albuterol is 68 times more effective in the treatment of asthma than the S enantiomer. **(See Example 10.1)**



(*R*)-Epinephrine
(Adrenaline)



(*R*)-Albuterol

(a) Classify each amino group as primary, secondary, or tertiary.
(b) List the similarities and differences between the structural formulas of these compounds.

10.16 There are eight constitutional isomers with the molecular formula $C_4H_{11}N$. Name and draw structural formulas for each. Classify each amine as primary, secondary, or tertiary. **(See Examples 10.1–10.3)**

10.17 Draw a structural formula for each compound with the given molecular formula: **(See Example 10.3)**

(a) A 2° arylamine, C_7H_9N
(b) A 3° arylamine, $C_8H_{11}N$
(c) A 1° aliphatic amine, C_7H_9N
(d) A chiral 1° amine, $C_4H_{11}N$
(e) A 3° heterocyclic amine, $C_5H_{11}N$
(f) A trisubstituted 1° arylamine, $C_9H_{13}N$
(g) A chiral quaternary ammonium salt, $C_9H_{22}NCl$

Physical Properties

10.18 Propylamine, ethylmethylamine, and trimethylamine are constitutional isomers with the molecular formula C_3H_9N: **(See Example 10.4)**

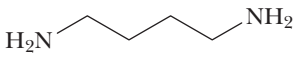
$CH_3CH_2CH_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3N$
bp 48 °C	bp 37 °C	bp 3 °C
Propylamine	Ethylmethylamine	Trimethylamine

Account for the fact that trimethylamine has the lowest boiling point of the three, and propylamine has the highest.

10.19 Account for the fact that 1-butanamine has a lower boiling point than 1-butanol: **(See Example 10.4)**

bp 78 °C	bp 117 °C
1-Butanamine	1-Butanol

***10.20** Account for the fact that putrescine, a foul-smelling compound produced by rotting flesh, ceases to smell upon treatment with two equivalents of HCl: **(See Example 10.4)**

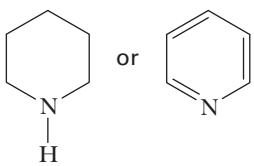


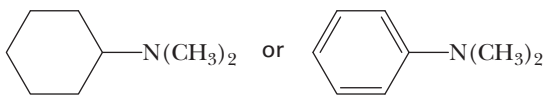
1,4-Butanediamine
(Putrescine)

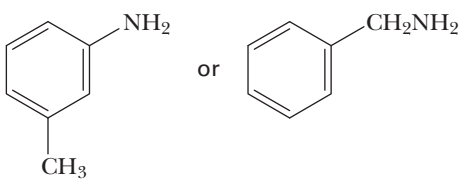
Basicity of Amines

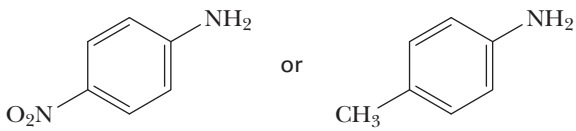
10.21 Account for the fact that amines are more basic than alcohols. **(See Example 10.6)**

10.22 From each pair of compounds, select the stronger base: **(See Example 10.6)**

(a) 

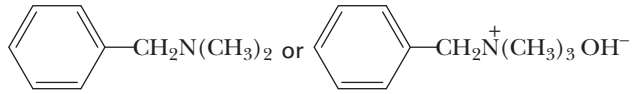
(b) 

(c) 

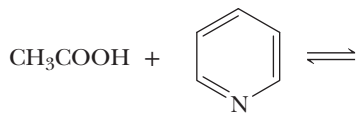
(d) 

10.23 Account for the fact that substitution of a nitro group makes an aromatic amine a weaker base, but makes a phenol a stronger acid. For example, 4-nitroaniline is a weaker base than aniline, but 4-nitrophenol is a stronger acid than phenol. **(See Example 10.6)**

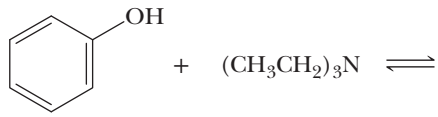
10.24 Select the stronger base in this pair of compounds: **(See Example 10.6)**



10.25 Complete the following acid–base reactions and predict the position of equilibrium for each. Justify your prediction by citing values of pK_a for the stronger and weaker acid in each equilibrium. For values of acid ionization constants, consult Table 2.2 (pK_a's of Some Inorganic and Organic Acids), Table 8.2 (pK_a's of Alcohols), Section 9.8B (Acidity of Phenols), and Table 10.2 (Base Strengths of Amines). Where no ionization constants are given, make the best estimate from aforementioned tables and section. **(See Examples 10.5–10.7)**

(a) 

Acetic acid Pyridine

(b) 

Phenol Triethylamine

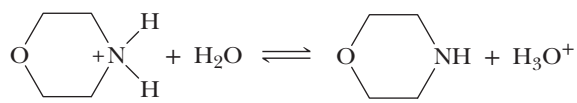
(c) 

1-Phenyl-2-propanamine (Amphetamine) 2-Hydroxypropanoic acid (Lactic acid)

(d) 

Methamphetamine Acetic acid

10.26 The pK_a of the morpholinium ion is 8.33:



Morpholinium ion
pK_a = 8.33

Morpholine

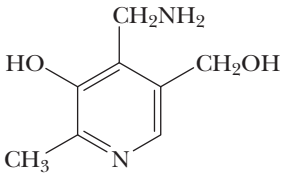
(a) Calculate the ratio of morpholine to morpholinium ion in aqueous solution at p*H* 7.0.

(b) At what p*H* are the concentrations of morpholine and morpholinium ion equal?

***10.27** The pK_b of amphetamine (Example 10.2e) is approximately 3.2. Calculate the ratio of amphetamine to its conjugate acid at p*H* 7.4, the p*H* of blood plasma.

10.28 Calculate the ratio of amphetamine to its conjugate acid at p*H* 1.0, such as might be present in stomach acid.

***10.29** Following is a structural formula of pyridoxamine, one form of vitamin B_6: **(See Examples 10.6, 10.7)**

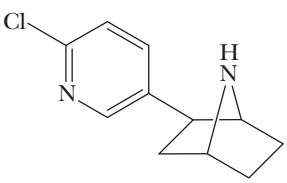


Pyridoxamine
(Vitamin B_6)

(a) Which nitrogen atom of pyridoxamine is the stronger base?

(b) Draw the structural formula of the hydrochloride salt formed when pyridoxamine is treated with one equivalent of HCl.

***10.30** Epibatidine, a colorless oil isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolor*, has several times the analgesic potency of morphine. It is the first chlorine-containing, nonopioid (nonmorphine-like in structure) analgesic ever isolated from a natural source: **(See Example 10.6)**



Epibatidine

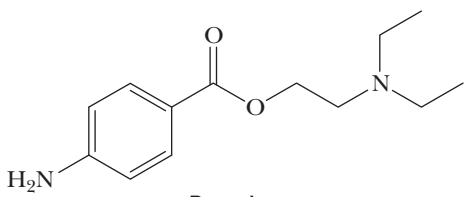
Stephen J. Krasemann/Photo Researchers

Poison arrow frog.

(a) Which of the two nitrogen atoms of epibatidine is the more basic?

(b) Mark all stereocenters in this molecule.

***10.31** Procaine was one of the first local anesthetics for infiltration and regional anesthesia: **(See Examples 10.6, 10.7)**



Procaine

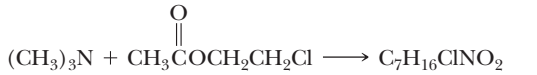
The hydrochloride salt of procaine is marketed as Novocaine®.

(a) Which nitrogen atom of procaine is the stronger base?

(b) Draw the formula of the salt formed by treating procaine with one mole of HCl.

(c) Is procaine chiral? Would a solution of Novocaine® in water be optically active or optically inactive?

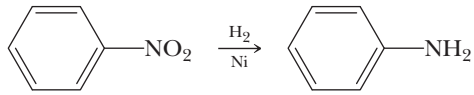
***10.32** Treatment of trimethylamine with 2-chloroethyl acetate gives the neurotransmitter acetylcholine as its chloride salt: **(See Example 10.7)**



Acetylcholine chloride

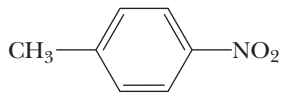
Propose a structural formula for this quaternary ammonium salt and a mechanism for its formation.

10.33 Aniline is prepared by the catalytic reduction of nitrobenzene:

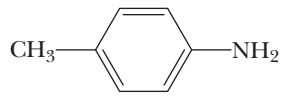


Devise a chemical procedure based on the basicity of aniline to separate it from any unreacted nitrobenzene.

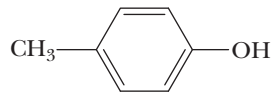
10.34 Suppose that you have a mixture of the following three compounds:



4-Nitrotoluene
(*p*-Nitrotoluene)



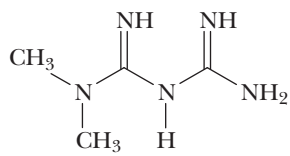
4-Methylaniline
(*p*-Toluidine)



4-Methylphenol
(*p*-Cresol)

Devise a chemical procedure based on their relative acidity or basicity to separate and isolate each in pure form.

***10.35** Following is a structural formula for metformin, the hydrochloride salt of which is marketed as the antidiabetic Glucophage®: **(See Example 10.7)**



Metformin

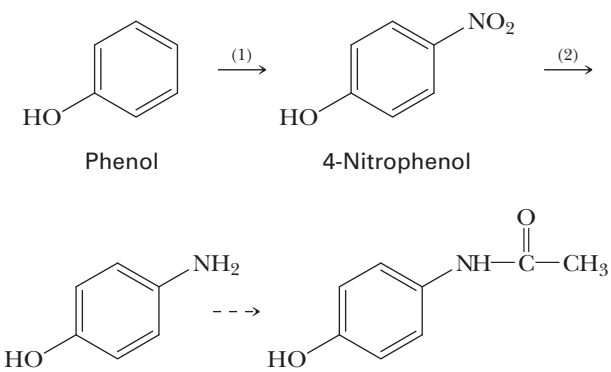
Metformin was introduced into clinical medicine in the United States in 1995 for the treatment of type 2 diabetes. More than 25 million prescriptions for this drug were written in 2000, making it the most commonly prescribed brand-name diabetes medication in the nation.

(a) Draw the structural formula for Glucophage®.

(b) Would you predict Glucophage® to be soluble or insoluble in water? Soluble or insoluble in blood plasma? Would you predict it to be soluble or insoluble in diethyl ether? In dichloromethane? Explain your reasoning.

Synthesis

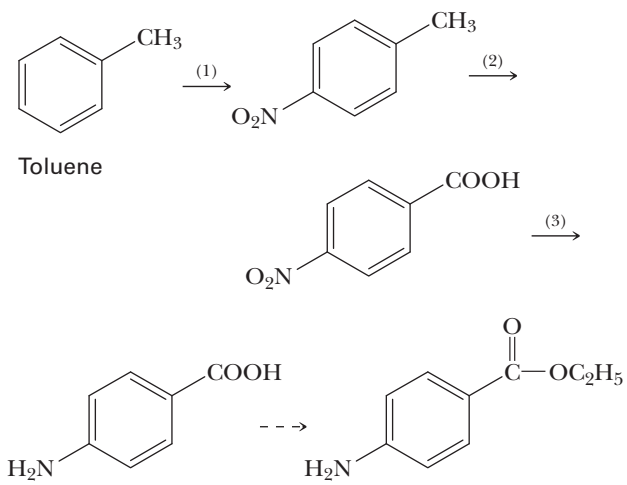
***10.36** 4-Aminophenol is a building block in the synthesis of the analgesic acetaminophen. Show how this building block can be synthesized in two steps from phenol (in Chapter 15, we will see how to complete the synthesis of acetaminophen): **(See Example 10.9)**



Phenol — 4-Nitrophenol

4-Aminophenol — Acetaminophen

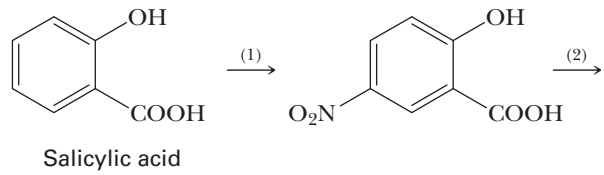
***10.37** 4-Aminobenzoic acid is a building block in the synthesis of the topical anesthetic benzocaine. Show how this building block can be synthesized in three steps from toluene (in Chapter 14, we will see how to complete the synthesis of benzocaine): **(See Example 10.9)**



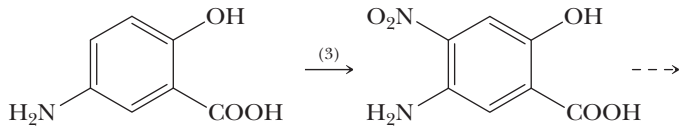
Toluene

4-Aminobenzoic acid — Ethyl 4-aminobenzoate (Benzocaine)

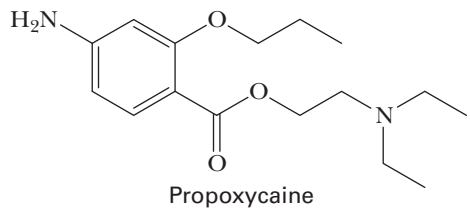
***10.38** The compound 4-amino-5-nitrosalicylic acid is one of the building blocks needed for the synthesis of propoxycaine, one of the family of "caine" anesthetics. Some other members of this family of local anesthetics are procaine (Novocaine®), lidocaine (Xylocaine®), and mepivicaine (Carbocaine®). 4-Amino-5-nitrosalicylic acid is synthesized from salicylic acid in three steps: **(See Example 10.9)**



Salicylic acid



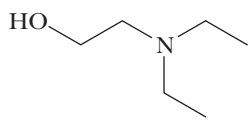
4-Amino-5-nitrosalicylic acid



Propoxycaine

Show reagents that will bring about the synthesis of 4-amino-5-nitrosalicylic acid.

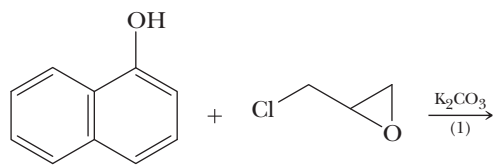
***10.39** A second building block for the synthesis of propoxycaine is 2-diethylaminoethanol:



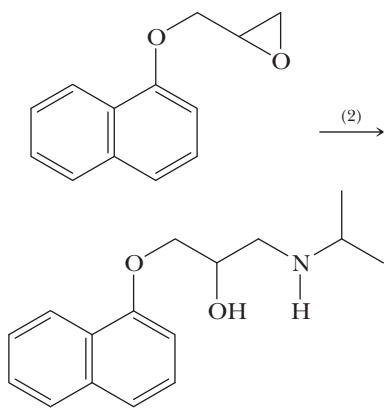
2-Diethylaminoethanol

Show how this compound can be prepared from ethylene oxide and diethylamine.

***10.40** Following is a two-step synthesis of the antihypertensive drug propranolol, a so-called beta blocker with vasodilating action:



1-Naphthol — Epichlorohydrin



Propranolol (Cardinol)

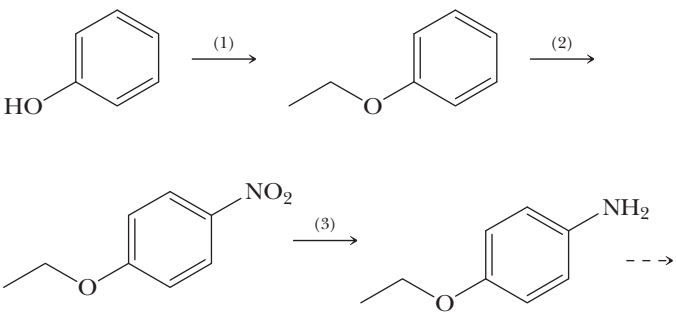
Propranolol and other beta blockers have received enormous clinical attention because of their effectiveness in treating hypertension (high blood pressure), migraine headaches, glaucoma, ischemic heart disease, and certain cardiac arrhythmias. The hydrochloride salt of propranolol has been marketed under at least 30 brand names, one of which is Cardinol®. (Note the "card-" part of the name, after *cardiac*.)

(a) What is the function of potassium carbonate, K_2CO_3, in Step 1? Propose a mechanism for the formation of the new oxygen–carbon bond in this step.

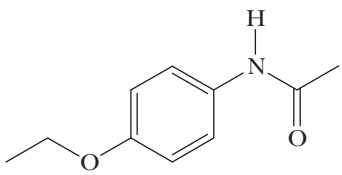
(b) Name the amine used to bring about Step 2, and propose a mechanism for this step.

(c) Is propranolol chiral? If so, how many stereoisomers are possible for it?

***10.41** The compound 4-ethoxyaniline, a building block of the over-the-counter analgesic phenacetin, is synthesized in three steps from phenol: **(See Example 10.9)**



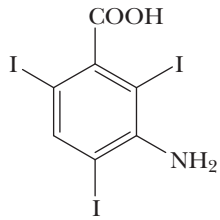
4-Ethoxyaniline



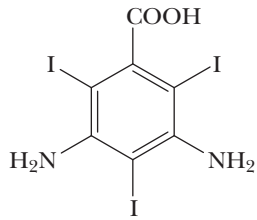
Phenacetin

Show reagents for each step of the synthesis of 4-ethoxyaniline. (In Chapter 14, we will see how to complete this synthesis.)

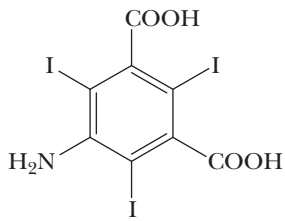
***10.42** Radiopaque imaging agents are substances administered either orally or intravenously that absorb X rays more strongly than body material does. One of the best known of these agents is barium sulfate, the key ingredient in the "barium cocktail" used for imaging of the gastrointestinal tract. Among other X-ray imaging agents are the so-called triiodoaromatics. You can get some idea of the kinds of imaging for which they are used from the following selection of trade names: Angiografin®, Gastrografin®, Cardiografin®, Cholografin®, Renografin®, and Urografin®. The most common of the triiodiaromatics are derivatives of these three triiodobenzene-carboxylic acids: **(See Example 10.9)**



3-Amino-2,4,6-triiodobenzoic acid

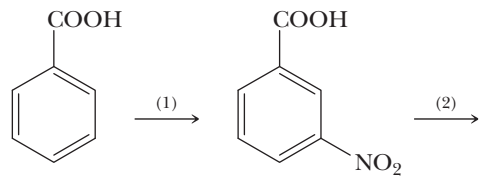


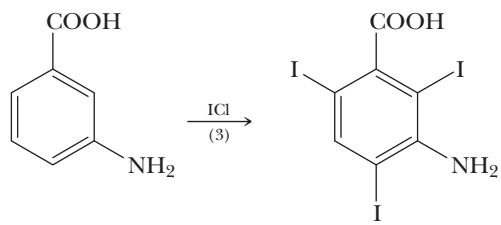
3,5-Diamino-2,4,6-triiodobenzoic acid



5-Amino-2,4,6-triiodoisophthalic acid

3-Amino-2,4,6-triiodobenzoic acid is synthesized from benzoic acid in three steps:





3-Amino-benzoic acid

3-Amino-2,4,6-triiodobenzoic acid

(a) Show reagents for Steps (1) and (2).

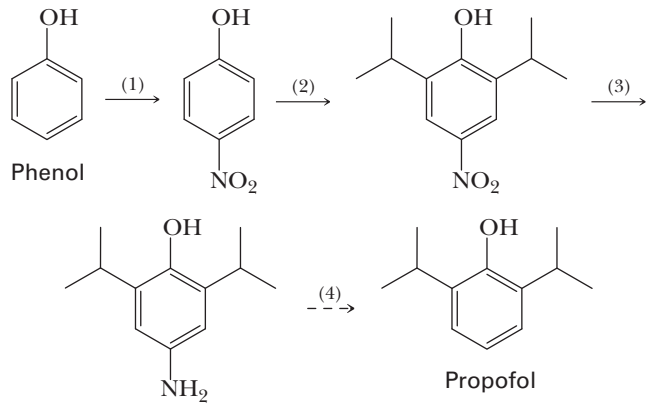
(b) Iodine monochloride, ICl, a black crystalline solid with a melting point of 27.2°C and a boiling point of 97°C, is

prepared by mixing equimolar amounts of I_2 and Cl_2. Propose a mechanism for the iodination of 3-aminobenzoic acid by this reagent.

(c) Show how to prepare 3,5-diamino-2,4,6-triiodobenzoic acid from benzoic acid.

(d) Show how to prepare 5-amino-2,4,6-triiodoisophthalic acid from isophthalic acid (1,3-benzenedicarboxylic acid).

***10.43** The intravenous anesthetic propofol is synthesized in four steps from phenol: **(See Example 10.9)**

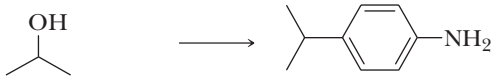


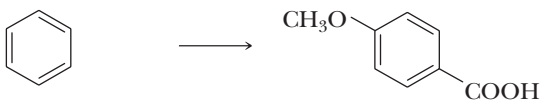
4-Amino-2,6-diisopropylphenol

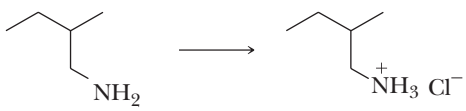
Show reagents to bring about steps 1–3.

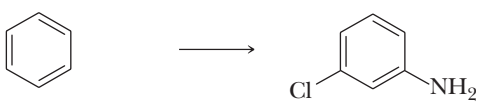
CHEMICAL TRANSFORMATIONS

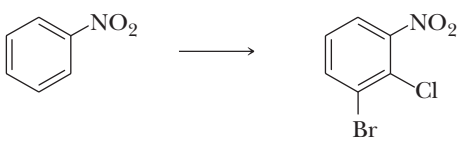
10.44 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note: Some will require more than one step.* **(See Example 10.9)**

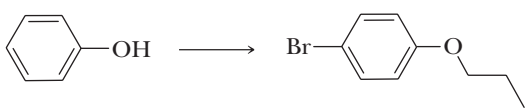
(a) 

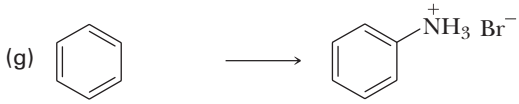
(b) 

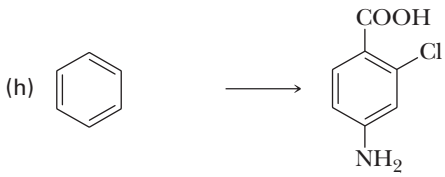
(c) 

(d) 

(e) 

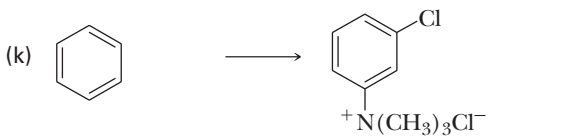
(f) 

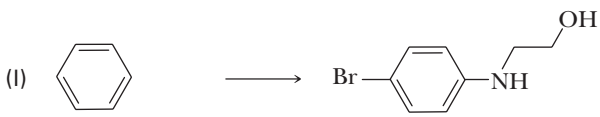
(g) 

(h) 

(i) 

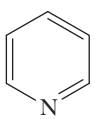
(j) 

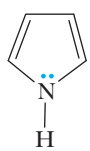
(k) 

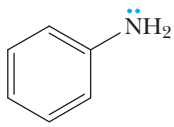
(l) 

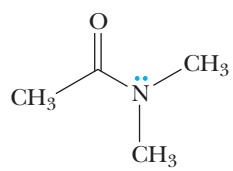
LOOKING AHEAD

10.45 State the hybridization of the nitrogen atom in each of the following compounds:

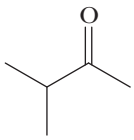
(a) 

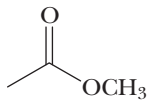
(b) 

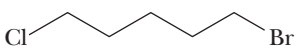
(c) 

(d) 

10.46 Amines can act as nucleophiles. For each of the following molecules, circle the most likely atom that would be attacked by the nitrogen of an amine:

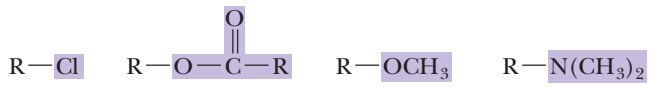
(a) 

(b) 

(c) 

10.47 Draw a Lewis structure for a molecule with the formula C_3H_7N that does not contain a ring or an alkene (a carbon–carbon double bond).

10.48 Rank the following leaving groups in order from best to worst:



GROUP LEARNING ACTIVITIES

10.49 Discuss why $-NH_2$ is a stronger base than $-OH$. Are both bases strong enough to quantitatively (100%) abstract the hydrogen from a terminal alkyne? Why or why not?

10.50 Take turns listing all of the factors that affect the basicity of an atom in an organic molecule. Then do the same for acidity, nucleophilicity, and leaving group ability. Which factors are common to all four properties? Take turns providing molecules that are good or strong examples of each (e.g., a strong base, a good nucleophile, etc.). Then do the same for weak examples of each.

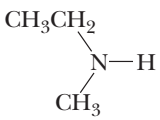
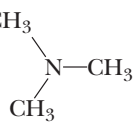
10.51 Compare the basicity of amide nitrogens to that of amines.

PUTTING IT TOGETHER

The following problems bring together concepts and material from Chapters 7–10. Although the focus may be on these chapters, the problems will also build on concepts discussed throughout the text thus far.

Choose the best answer for each of the following questions.

1. Arrange the following amines from lowest to highest boiling point.

A  **B**  **C** 

(a) **A, B, C** (c) **B, C, A** (e) **C, A, B**
(b) **C, B, A** (d) **B, A, C**

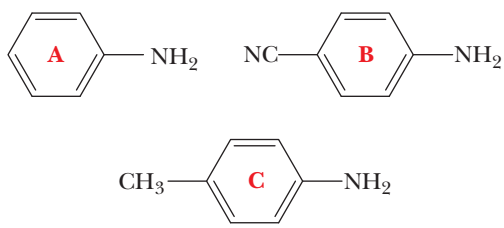
2. Which of the following statements is true regarding the following two molecules?

(a) Both **A** and **B** are aromatic.
(b) Both **A** and **B** are aliphatic amines.
(c) The nitrogen atoms in **A** and **B** are both sp^3 hybridized.
(d) **B** is more basic than **A**.
(e) Both **A** and **B** are planar molecules.

3. Which series of reagents can be used to achieve the following transformation?

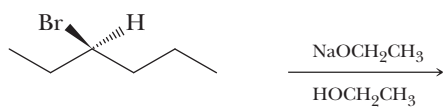
(a) 1) HBr 2) H_2SO_4
(b) 1) H_2SO_4, H_2O 2) PCC
(c) 1) HCl 2) $SOCl_2$
(d) 1) H_3PO_4, H_2O 2) H_2CrO_4
(e) More than one of these will achieve the transformation.

4. Arrange the following from strongest to weakest base.



(a) **A, B, C** (b) **B, C, A** (c) **C, A, B** (d) **A, C, B** (e) **B, A, C**

5. How many products are possible from the following elimination reaction?



(a) one (b) two (c) three (d) four (e) six

6. Which series of reagents can be used to achieve the following transformation?

(a) 1) HCl 2) RCO_3H

(b) 1) $SOCl_2$ 2) RCO_3H

(c) 1) Na 2) RCO_3H

(d) 1) H_3PO_4 2) RCO_3H

(e) 1) H_2CrO_4 2) RCO_3H

7. Consider the following situation: An ether solution containing phenol and a neutral compound is extracted with 30% sodium bicarbonate. Next the ether solution is extracted with 30% NaOH. Finally, the ether solution is extracted with distilled water. Which solution contains the phenol?

(a) The 30% sodium bicarbonate solution.

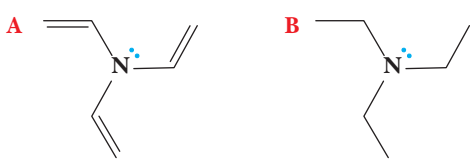
(b) The 30% NaOH solution.

(c) The ether.

(d) The distilled water.

(e) Not enough information to determine.

8. Which of the following statements is true concerning the following two molecules?



(a) Both are aromatic.

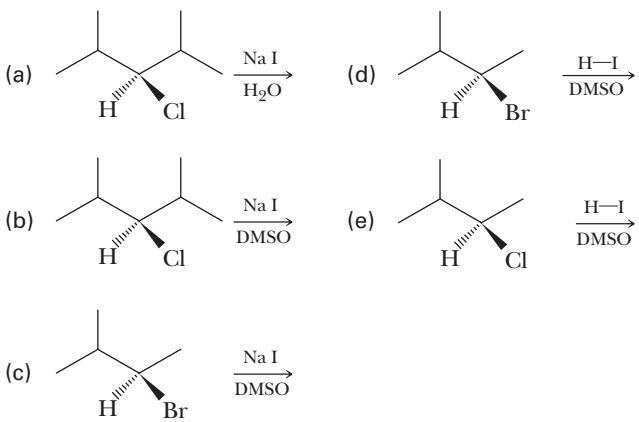
(b) Only one molecule is an amine.

(c) **B** is more polar than **A**.

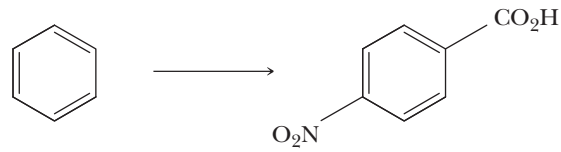
(d) **A** is more basic than **B**.

(e) All of these statements are true.

9. Which combination of reagents would be most likely to undergo an S_N2 reaction?



10. Which series of reagents can be used to achieve the following transformation?



(a) 1) $CH_3Br/FeBr_3$ 2) H_2SO_4/HNO_3 3) H_2CrO_4

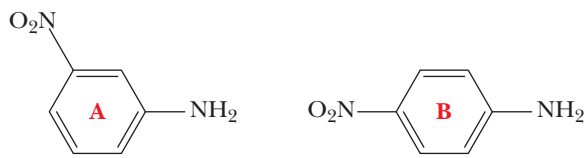
(b) 1) H_2SO_4/HNO_3 2) H_2CrO_4 3) $CH_3Br/FeBr_3$

(c) 1) $H_2SO_4/K_2Cr_2O_4$ 2) $CH_3Br/FeBr_3$ 3) H_2SO_4/HNO_3

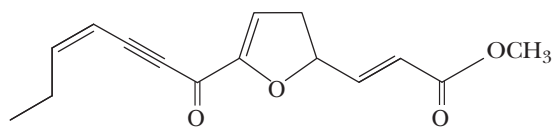
(d) 1) $CH_3Br/FeBr_3$ 2) H_2CrO_4 3) H_2SO_4/HNO_3

(e) 1) H_2SO_4/HNO_3 2) $CH_3Br/FeBr_3$ 3) H_2CrO_4

11. Determine which aryl amine (**A** or **B**) is more basic and provide a rationale for your determination.



12. Answer the questions that follow regarding the compound Wyerone, which is obtained from fava beans (*Vicia faba*) and has been found to possess antifungal properties.



Wyerone

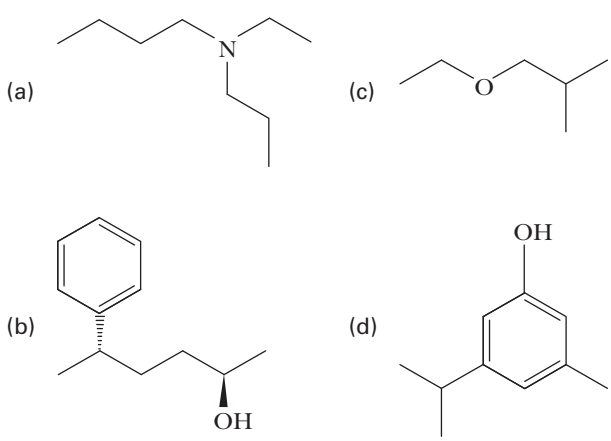
(a) Would you expect the compound to be soluble in water?

(b) How many stereoisomers exist for the compound shown?

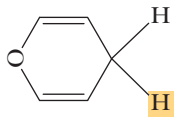
(c) Is the molecule chiral?

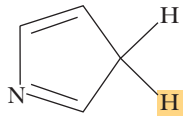
(d) How many equivalents of Br_2 in CH_2Cl_2 would Wyerone be expected to react with?

13. Provide IUPAC names for the following compounds.



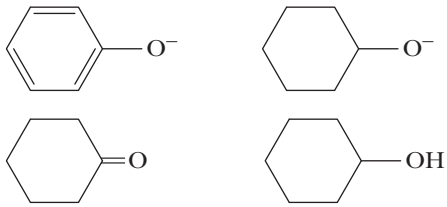
14. Determine whether highlighted proton **A** or **B** is more acidic and provide a rationale for your selection.

(a) 

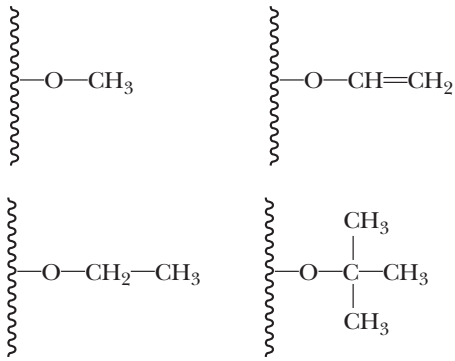
(b) 

15. Select the answer that best fits each description and provide an explanation for your decision.

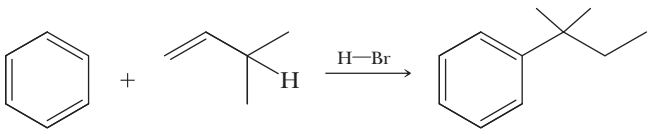
(a) The best nucleophile



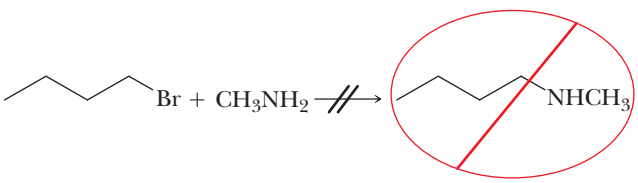
(b) The best leaving group



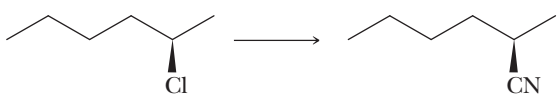
16. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.



17. When the following nucleophilic substitution reaction was performed, the major product was found to possess the molecular formula $C_{13}H_{30}N$ rather than $C_5H_{13}N$, the formula of the desired product shown below. Provide the structure of the major product and explain why it is formed over the desired product.

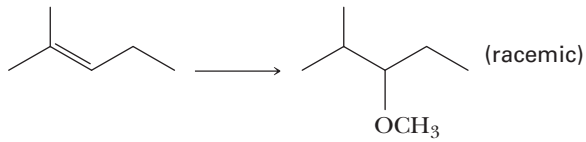


18. Complete the following chemical transformations

(a) 

This enantiomer as the *only* product

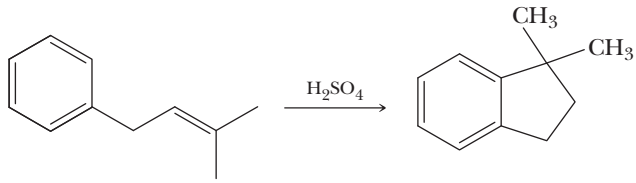
(b) 

(c) 

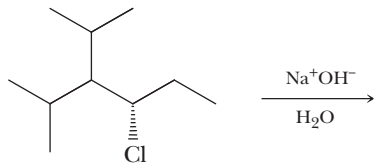
(racemic)

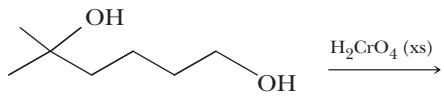
(d) 

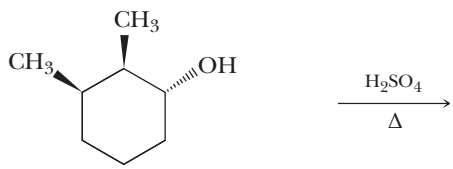
19. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.

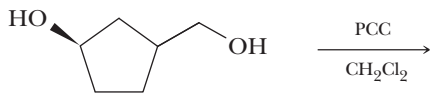


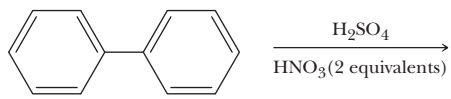
20. Predict the major product or products of each of the following reactions. Be sure to consider stereochemistry in your answers.

(a) 

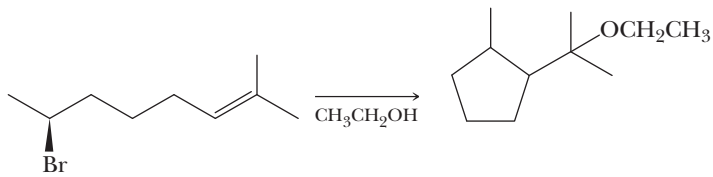
(b) 

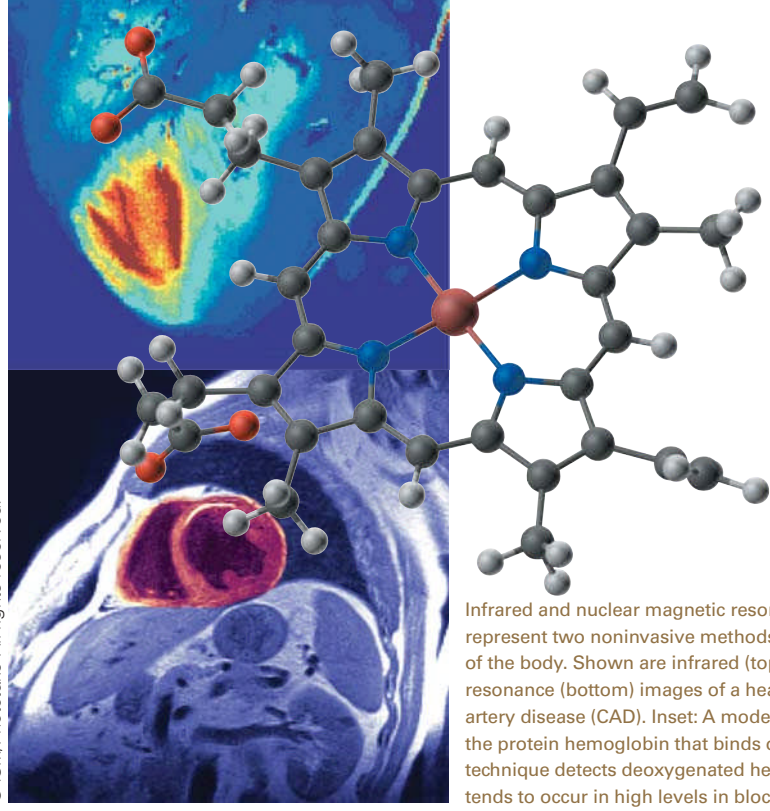
(c) 

(d) 

(e) 

21. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.





Spectroscopy

Infrared and nuclear magnetic resonance imaging represent two noninvasive methods for medical imaging of the body. Shown are infrared (top) and magnetic resonance (bottom) images of a heart with coronary artery disease (CAD). Inset: A model of heme, the part of the protein hemoglobin that binds oxygen. The infrared technique detects deoxygenated hemoglobin, which tends to occur in high levels in blocked arteries.

11

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

DETERMINING THE MOLECULAR structure of a compound is a central theme in science. In medicine, for example, the structure of any drug must be known before it can be approved for use in patients. In the biotechnology and pharmaceutical industries, knowledge of a compound's structure can provide new leads to promising therapeutics. In organic chemistry, knowledge of the structure of a compound is essential to its use as a reagent or a precursor to other molecules.

Chemists rely almost exclusively on instrumental methods of analysis for structure determination. A number of these methods utilize **spectroscopy**, the interaction of matter with electromagnetic radiation, and the two forms of spectroscopy we will study are infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy. These two commonly used techniques provide a wealth of information about the structure of a compound. But before we discuss these techniques, we will first review some of the fundamentals of electromagnetic radiation.

Spectroscopy The study of the interaction of matter and electromagnetic radiation.

11.1 What Is Electromagnetic Radiation?

Electromagnetic radiation Light and other forms of radiant energy.

Wavelength (λ) The distance between two consecutive identical points on a wave.

Frequency (ν) A number of full cycles of a wave that pass a point in a second.

Hertz The unit in which wave frequency is reported; s^{-1} (read *per second*).

Gamma rays, X rays, ultraviolet light, visible light, infrared radiation, microwaves, and radio waves are all part of the electromagnetic spectrum. Because **electromagnetic radiation** behaves as a wave traveling at the speed of light, it is described in terms of its wavelength and frequency. Table 11.1 summarizes the wavelengths, frequencies, and energies of some regions of the electromagnetic spectrum.

Wavelength is the distance between any two consecutive identical points on the wave. Wavelength is given the symbol λ (Greek lowercase lambda) and is usually expressed in the SI base unit of meters. Other derived units commonly used to express wavelength are given in Table 11.2.

The **frequency** of a wave is the number of full cycles of the wave that pass a given point in a second. Frequency is given the symbol ν (Greek nu) and is reported in **hertz** (Hz), which has the unit of reciprocal seconds (s^{-1}). Wavelength and frequency are inversely proportional, and we can calculate one from the other from the relationship

$$\nu\lambda = c$$

TABLE 11.1 Wavelength, Frequency, and Energy Relationships of Some Regions of the Electromagnetic Spectrum

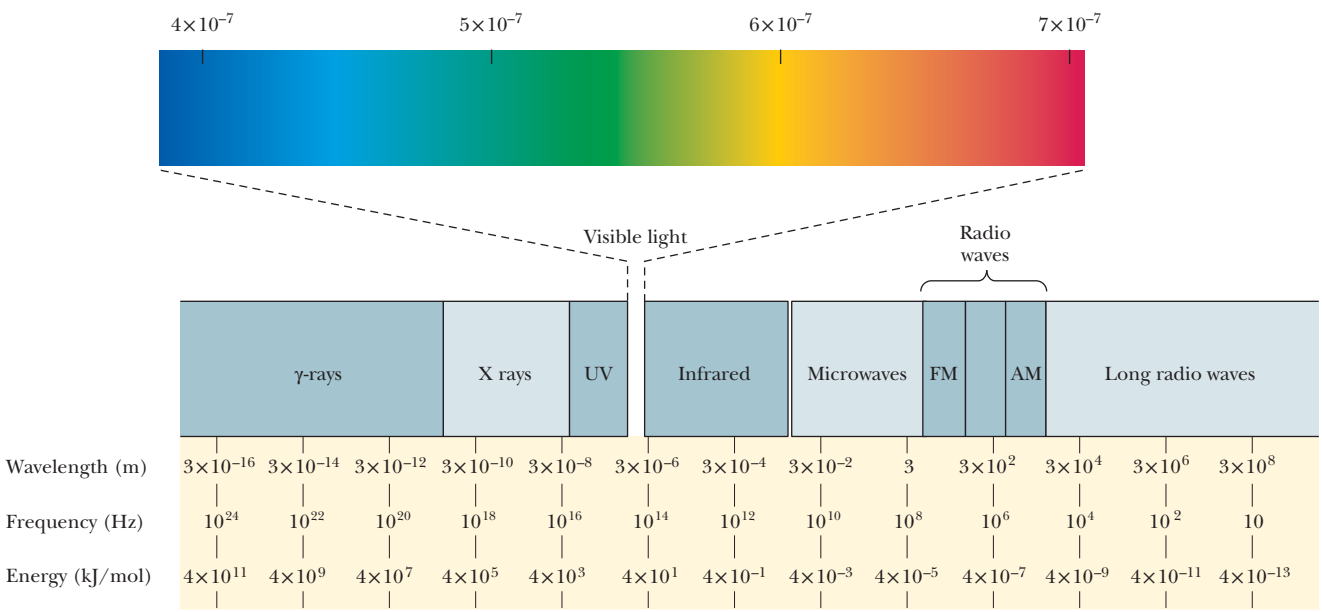
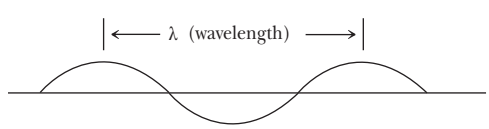


TABLE 11.2 Common Units Used to Express Wavelength (λ)

Unit	Relation to Meter
meter (m)	———
millimeter (mm)	$1\,mm = 10^{-3}\,m$
micrometer (μm)	$1\,\mu m = 10^{-6}\,m$
nanometer (nm)	$1\,nm = 10^{-9}\,m$
Angstrom (Å)	$1\,Å = 10^{-10}\,m$



where ν is frequency in hertz, c is the velocity of light (3.00×10^8 m/s), and λ is the wavelength in meters. For example, consider infrared radiation—or heat radiation, as it is also called—with wavelength 1.5×10^{-5} m. The frequency of this radiation is

$$\nu = \frac{3.0 \times 10^8 \text{ m/s}}{1.5 \times 10^{-5} \text{ m}} = 2.0 \times 10^{13} \text{ Hz}$$

An alternative way to describe electromagnetic radiation is in terms of its properties as a stream of particles. We call these particles **photons**. The energy in a mole of photons and the frequency of radiation are related by the equation

$$E = h\nu = h\frac{c}{\lambda}$$

these equations show that electromagnetic radiation are forms of energy. We will see that molecules interact with different forms of electromagnetic radiation by absorbing their energy in various ways

where E is the energy in kJ/mol and h is Planck's constant, 3.99×10^{-13} kJ·s·mol^{-1} (9.54×10^{-14} kcal·s·mol^{-1}). This equation tells us that high-energy radiation corresponds to short wavelengths, and vice versa. Thus, ultraviolet light (higher energy) has a shorter wavelength (approximately 10^{-7} m) than infrared radiation (lower energy), which has a wavelength of approximately 10^{-5} m.

EXAMPLE 11.1

Calculate the energy, in kiloJoules per mole of radiation, of a wave with wavelength 2.50 μm. What type of radiant energy is this? (Refer to Table 11.1.)

STRATEGY

Use the relationship $E = hc/\lambda$. Make certain that the dimensions for distance are consistent: If the dimension of wavelength is meters, then express the velocity of light in meters per second.

SOLUTION

First convert 2.50 μm to meters, using the relationship 1 μm = 10^{-6} m (Table 11.2):

$$2.50 \ \mu\text{m} \times \frac{10^{-6} \text{ m}}{1 \ \mu\text{m}} = 2.50 \times 10^{-6} \text{ m}$$

Now substitute this value into the equation $E = hc/\lambda$:

$$E = \frac{hc}{\lambda} = 3.99 \times 10^{-13} \frac{\text{kJ} \cdot \text{s}}{\text{mol}} \times 3.00 \times 10^8 \frac{\text{m}}{\text{s}} \times \frac{1}{2.50 \times 10^{-6} \text{ m}}$$
$$= 47.7 \text{ kJ/mol } (11.4 \text{ kcal/mol})$$

Electromagnetic radiation with energy of 47.7 kJ/mol is radiation in the infrared region.

See problems 11.18–11.20

PROBLEM 11.1

Calculate the energy of red light (680 nm) in kilocalories per mole. Which form of radiation carries more energy, infrared radiation with wavelength 2.50 μm or red light with wavelength 680 nm?

11.2 What Is Molecular Spectroscopy?

Organic molecules are flexible structures. They rotate in solution, their bonds stretch, bend, and rotate, and they contain electrons that can move from one electronic energy level to another. We know from experimental observations and from theories of molecular structure that all energy changes within a molecule are quantized; that is, they are subdivided into small, but well-defined, increments. For example, vibrations of bonds within molecules can undergo transitions only between allowed vibrational energy levels.

We can cause an atom or molecule to undergo a transition from energy state E_1 to a higher energy state E_2 by irradiating it with electromagnetic radiation corresponding to the energy difference between states E_1 and E_2, as illustrated schematically in Figure 11.1. When the atom or molecule returns to the ground state E_1, an equivalent amount of energy is emitted.

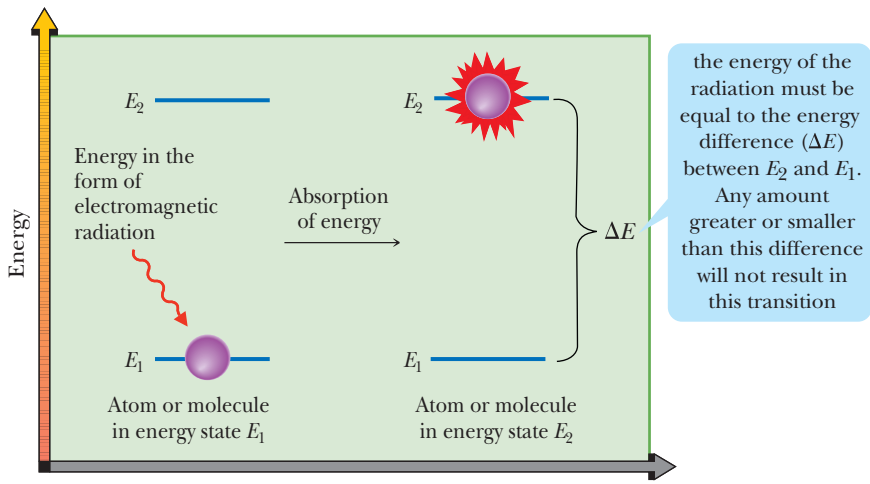


FIGURE 11.1 Absorption of energy in the form of electromagnetic radiation excites an atom or a molecule in energy state E_1 to a higher energy state E_2.

Molecular spectroscopy The study of the frequencies of electromagnetic radiation that are absorbed or emitted by substances and the correlation between these frequencies and specific types of molecular structure.

Molecular spectroscopy is the experimental process of measuring which frequencies of radiation a substance absorbs or emits and then correlating those frequencies with specific types of molecular structures. In **nuclear magnetic resonance (NMR) spectroscopy**, the compound is placed under the influence of a strong magnetic field and then irradiated with radio-frequency radiation, the absorption of which causes nuclei to be in a higher energy spin state. We will have more to say about NMR spectroscopy in Section 11.5. In **infrared (IR) spectroscopy**, we irradiate a compound with infrared radiation, the absorption of which causes covalent bonds to change from a lower vibrational energy level to a higher one. Because different functional groups have different bond strengths, the energy required to bring about these transitions will vary from one functional group to another. Thus, in infrared spectroscopy, we detect functional groups by the vibrations of their bonds.

11.3 What Is Infrared Spectroscopy?

A. The Vibrational Infrared Spectrum

Vibrational infrared The portion of the infrared region that extends from 4000 to 400 cm^{-1}.

Wavenumber ($\bar{\nu}$) A characteristic of electromagnetic radiation equal to the number of waves per centimeter.

In organic chemistry, we use a portion of the electromagnetic spectrum called the **vibrational infrared** region. This region extends from 2.5×10^{-6} to 25×10^{-6} m and corresponds to energies from 48–4.8 kJ/mol (11–1.2 kcal/mol). We commonly refer to radiation in the vibrational infrared region by its **wavenumber** ($\bar{\nu}$), the number of waves per centimeter:

$$\bar{\nu} = \frac{1}{\lambda\,(\text{cm})} = \frac{10^{-2}\,(\text{m}\cdot\text{cm}^{-1})}{\lambda\,(\text{m})}$$

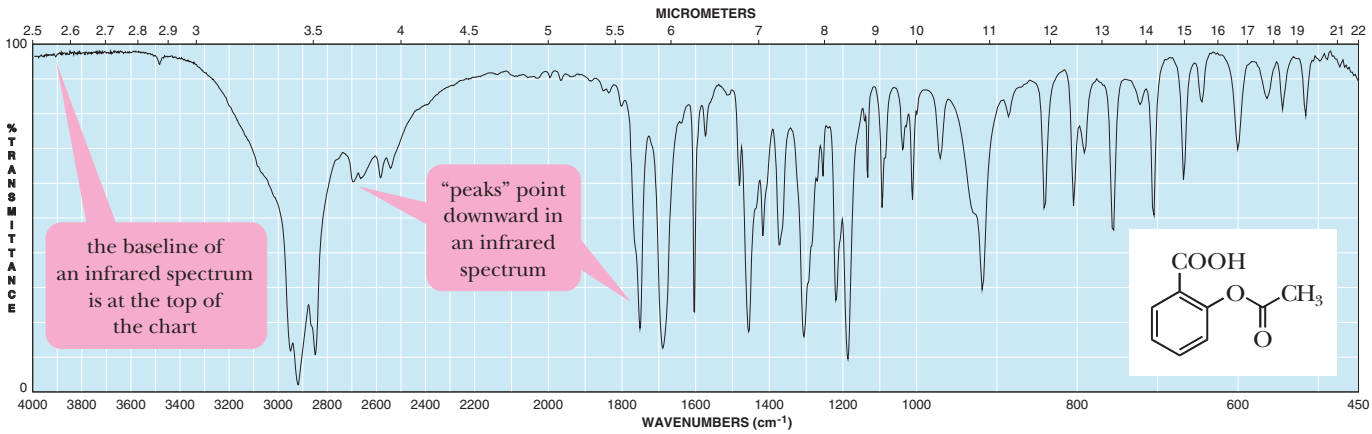


FIGURE 11.2 Infrared spectrum of aspirin.

Expressed in wavenumbers, the vibrational region of the infrared spectrum extends from 4000 to 400 cm^{-1} (the unit cm^{-1} is read "reciprocal centimeter"):

$$\bar{\nu} = \frac{10^{-2}\ \text{m} \cdot \text{cm}^{-1}}{2.5 \times 10^{-6}\ \text{m}} = 4000\ \text{cm}^{-1} \qquad \bar{\nu} = \frac{10^{-2}\ \text{m} \cdot \text{cm}^{-1}}{25 \times 10^{-6}\ \text{m}} = 400\ \text{cm}^{-1}$$

An advantage of using wavenumbers is that they are directly proportional to energy; the higher the wavenumber, the higher is the energy of radiation.

Figure 11.2 shows an infrared spectrum of aspirin. The horizontal axis at the bottom of the chart is calibrated in wavenumbers (cm^{-1}); that at the top is calibrated in wavelength (micrometers, μm). The vertical axis measures transmittance, with 100% transmittance at the top and 0% transmittance at the bottom. Thus, the baseline for an infrared spectrum (100% transmittance of radiation through the sample = 0% absorption) is at the top of the chart, and the absorption of radiation corresponds to a trough or valley. Strange as it may seem, we commonly refer to infrared absorptions as peaks, even though they are actually troughs.

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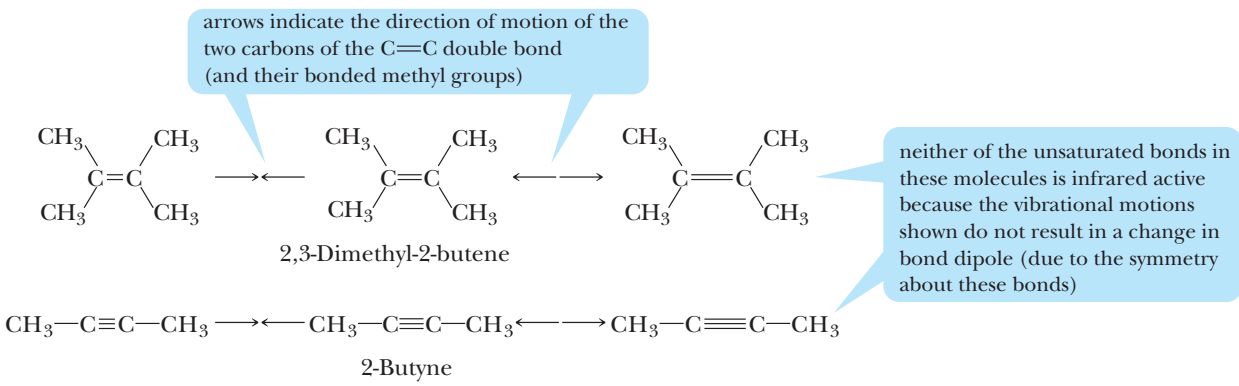
Humans cannot see infrared light without assistance from infrared sensors such as those present in night vision goggles and binoculars.

B. Molecular Vibrations

For a molecule to absorb infrared radiation, the bond undergoing vibration must be polar, and its vibration must cause a periodic change in the bond dipole; the greater the polarity of the bond, the more intense is the absorption. Any vibration that meets this criterion is said to be **infrared active**. Covalent bonds in homonuclear diatomic molecules, such as H_2 and Br_2, and some carbon–carbon double bonds in symmetrical alkenes and alkynes do not absorb infrared radiation because they are not polar bonds. The multiple bonds in the following two molecules, for example, do not have a dipole moment and, therefore, are not infrared active:



The simplest vibrational motions in molecules giving rise to the absorption of infrared radiation are **stretching** and **bending** motions. Illustrated in Figure 11.3 are the fundamental stretching and bending vibrations for a methylene group.

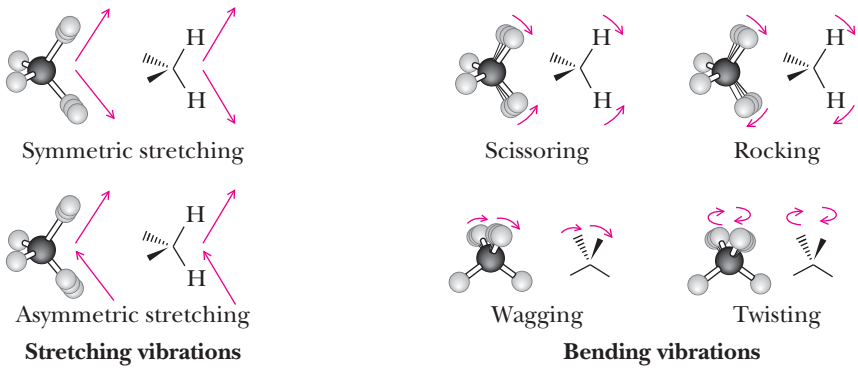


FIGURE 11.3 Fundamental modes of vibration for a methylene group.

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A Beckman Coulter DU 800 infrared spectrophotometer. Spectra are shown in the monitor.

To one skilled in the interpretation of infrared spectra, absorption patterns can yield a wealth of information about molecular structure. We, however, have neither the time nor the need to develop that level of competence. The value of infrared spectra for us is that we can use them to determine the presence or absence of particular functional groups. A carbonyl group, for example, typically shows strong absorption at approximately 1630–1800 cm^{-1}. The position of absorption for a particular carbonyl group depends on (1) whether it is that of an aldehyde, a ketone, a carboxylic acid, an ester, or an amide, and (2) if the carbonyl carbon is in a ring, the size of the ring.

C. Correlation Tables

Data on absorption patterns of selected functional groups are collected in tables called **correlation tables**. Table 11.3 gives the characteristic infrared absorptions for the types of bonds and functional groups we deal with most often. Appendix 4 contains a more comprehensive correlation table. In these tables, we refer to the intensity of a particular absorption as **strong** (**s**), **medium** (**m**), or **weak** (**w**).

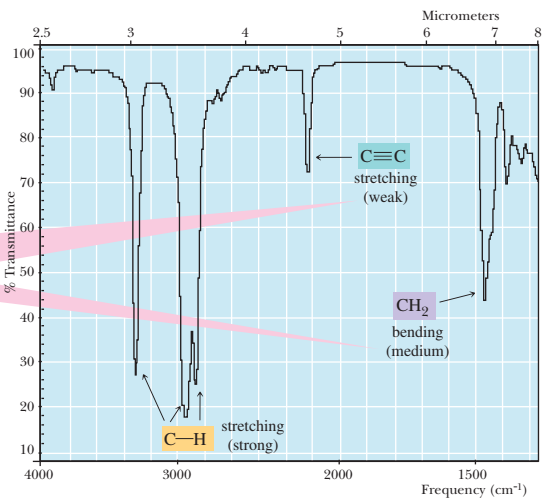
In general, we will pay most attention to the region from 3650 to 1000 cm^{-1} because the characteristic stretching vibrations for most functional groups are found in this region. Vibrations in the region from 1000 to 400 cm^{-1} are much more complex and far more difficult to analyze. It is often called the **fingerprint region** because even slight variations in molecular structure lead to differences in absorption patterns in this region. If two compounds have even slightly different structures, the differences in their infrared spectra are most clearly discernible in the fingerprint region.

Fingerprint region The portion of the vibrational infrared region that extends from 1000 to 400 cm^{-1} and that is unique to every compound.

TABLE 11.3 Characteristic IR Absorptions of Selected Functional Groups

Frequency range (cm^{-1})	Bond or functional group	Intensity
3500–3200	O—H alcohol	strong and broad
3400–2400	O—H carboxyl group	strong and broad
3500–3100	N—H amine	medium
3330–3270	≡C—H alkyne	medium
3100–3000	=C—H alkene	medium
3000–2850	—C—H alkane	medium to strong
2260–2100	C≡C alkyne	weak
1800–1630	C=O carbonyl	strong
1680–1600	C=C alkene	weak
1250–1050	C—O ether	strong

these descriptors refer to the intensity of the peak in an IR spectrum



EXAMPLE 11.2

Determine the functional group that is most likely present if IR absorption appears at
(a) 1705 cm^{-1} **(b)** 2200 cm^{-1}

STRATEGY

Refer to correlation Table 11.3. Eventually, through the continual practice of problems in this chapter, many of these vibrational stretching frequencies and intensities will become familiar to you.

SOLUTION

(a) A C═O group **(b)** a C—C triple bond

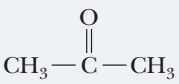
See problems 11.29–11.31

PROBLEM 11.2

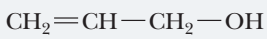
A compound shows strong, very broad IR absorption in the region from 3200 to 3500 cm^{-1} and strong absorption at 1715 cm^{-1}. What functional group accounts for both of these absorptions?

EXAMPLE 11.3

Propanone and 2-propen-1-ol are constitutional isomers. Show how to distinguish between these two isomers by IR spectroscopy.



Propanone
(Acetone)



2-Propen-1-ol
(Allyl alcohol)

STRATEGY

Because IR spectroscopy distinguishes between characteristic vibrational frequencies of differing *functional groups*, identify the *different* functional groups in the pair of molecules and predict (using correlation tables) the vibrational frequencies that these functional groups would exhibit in an IR spectrum.

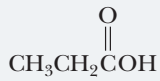
SOLUTION

Only propanone shows strong absorption in the C═O stretching region, 1630–1800 cm^{-1}. Alternatively, only 2-propen-1-ol shows strong absorption in the O—H stretching region, 3200–3500 cm^{-1}.

See problems 11.29–11.31

PROBLEM 11.3

Propanoic acid and methyl ethanoate are constitutional isomers. Show how to distinguish between these two compounds by IR spectroscopy.



Propanoic acid

Methyl ethanoate
(Methyl acetate)

11.4 How Do We Interpret Infrared Spectra?

Interpreting spectroscopic data is a skill that is easy to acquire through practice and exposure to examples. An IR spectrum will reveal not only the functional groups that are present in a sample, but also those that can be excluded from consideration. Often, we can determine the structure of a compound solely from the data in the spectrum of the compound and from information found in Table 11.3. Other times, we may need additional information, such as the molecular formula of the compound, or knowledge of the chemical reactions the molecule undergoes. In this section, we will see specific examples of IR spectra for characteristic functional groups. Familiarizing yourself with them will help you to master the technique of spectral interpretation.

Chemical Connections 11A

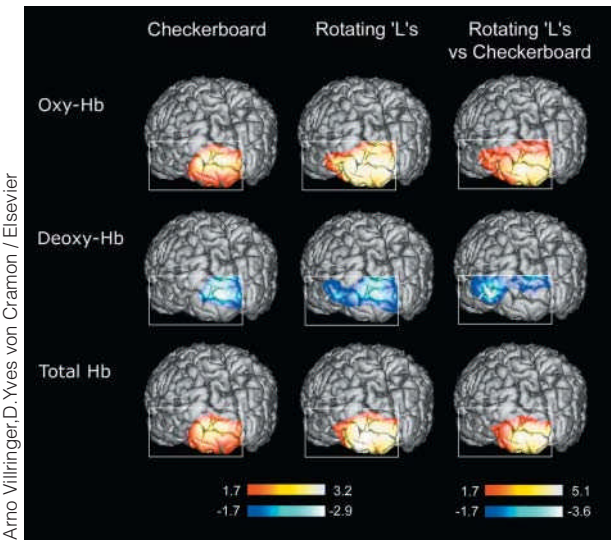
INFRARED SPECTROSCOPY: A WINDOW ON BRAIN ACTIVITY

Some of the great advantages of infrared spectroscopy are the relatively low cost, sensitivity, and speed of its instrumentation. The medical and scientific community recognized these benefits, along with the fact that some frequencies of infrared light can harmlessly penetrate human tissue and bone, in creating a technique called functional Near Infrared Spectroscopy (fNIRS). In fNIRS, a patient is fitted with headgear containing many fiber optic cables that allow infrared light in the 700–1000 nm range to be shone through the skull and into the brain. Separate fiber optic cables in the headgear collect the light that reemerges from the brain and direct it to a spectrophotometer, which quantifies the intensity of the light. The instrument measures changes in the concentration of oxygenated and deoxygenated hemoglobin, which absorbs light in the 700–1000 nm range. Because an assortment of tasks that the brain may be asked to carry out results in varying blood flow and oxygenation levels in different parts of the brain, fNIRS can be used to determine how certain thoughts or actions affect brain activity.

Questions

Could fNIRS be used to detect free oxygen (O_2) levels in the lungs? Why or why not?

AFP/Getty Images, Inc.



Matthias L. Schroeter, Markus M. Bücheler, Karsten Müller, Kâmil Uludağ, Helmuth Obrig, Gabriele Lohmann, Marc Tittgemeyer, Arno Villringer, D. Yves von Cramon / Elsevier

A research subject is asked to perform several mental tasks (left) while fNIRS analysis reveals varying levels of oxy- and deoxyhemoglobin in the blood flowing through the subject's brain.

A. Alkanes, Alkenes, and Alkynes

Figure 11.4 shows an infrared spectrum of decane. The strong peak with multiple splittings between 2850 and 3000 cm^{-1} is characteristic of alkane C—H stretching. The C—H peak is strong in this spectrum because there are so many C—H bonds and no other functional groups. Because alkane CH, CH_2, and CH_3 groups are present in most organic compounds, this peak is among the most commonly encountered in infrared spectroscopy.

Figure 11.5 shows the infrared spectrum of cyclopentene, which shows the easily recognized alkene stretching band slightly to the left of (at a greater wavenumber than) 3000 cm^{-1}. Also characteristic of alkenes is stretching at 1600 cm^{-1}. Notice that because cyclopentene has alkyl CH_2 groups, the characteristic alkane C—H stretching peak is also observed just below 3000 cm^{-1}.

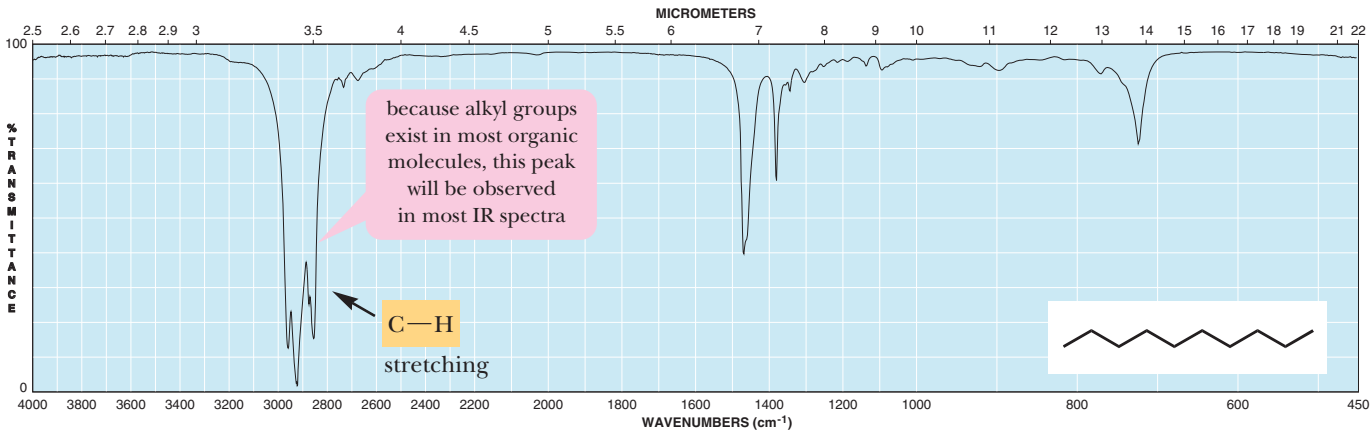


FIGURE 11.4 Infrared spectrum of decane.

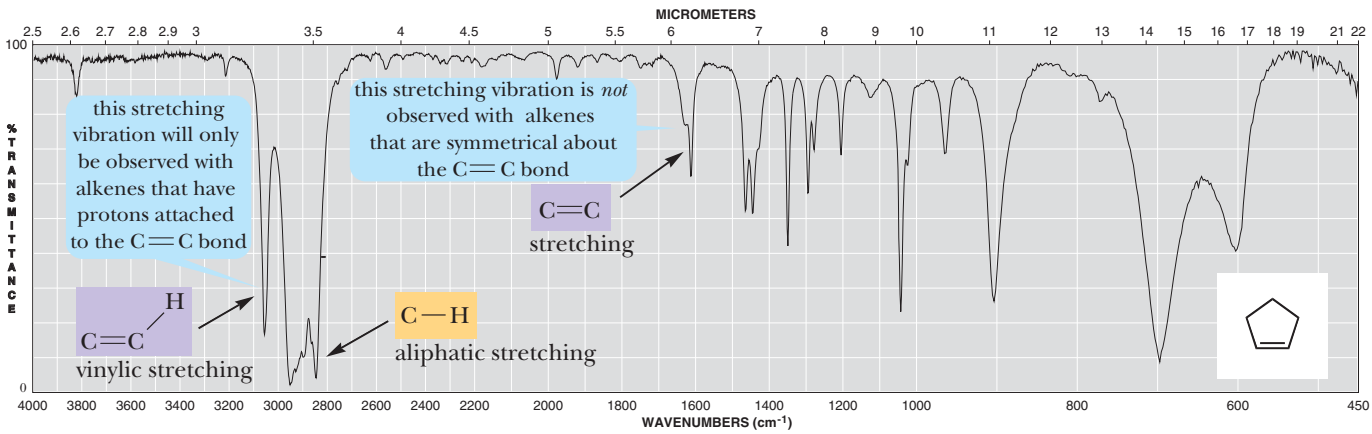


FIGURE 11.5 Infrared spectrum of cyclopentene.

Terminal alkynes exhibit C≡C—H stretching at 3300 cm^{-1}. This absorption band is absent in internal alkynes, because the triple bond is not bonded to a proton. All alkynes absorb weakly between 2100 and 2260 cm^{-1}, due to C≡C stretching. This stretching shows clearly in the spectrum of 1-octyne (Figure 11.6).

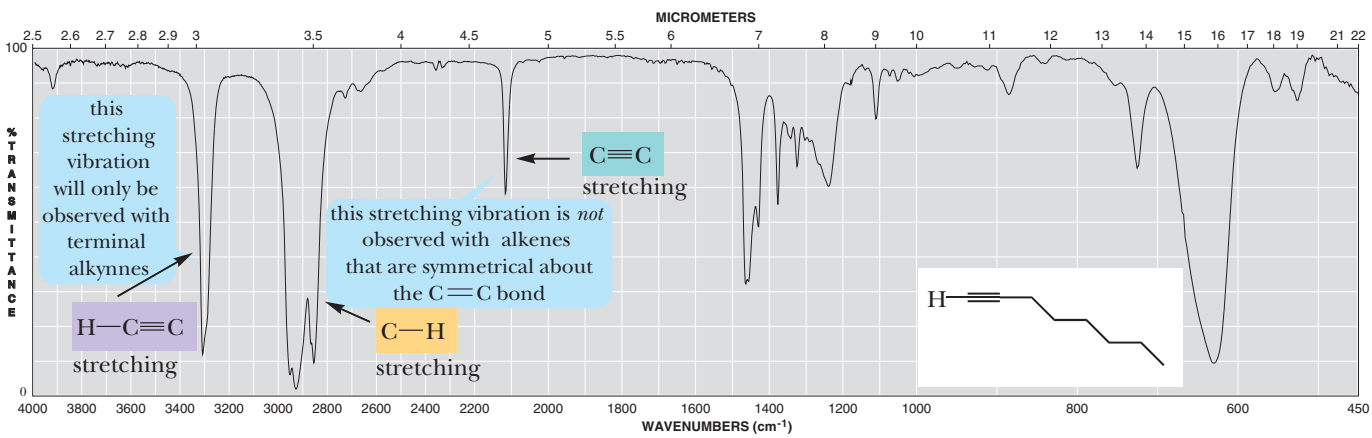


FIGURE 11.6 Infrared spectrum of 1-octyne.

B. Alcohols

Alcohols such as 1-pentanol are easily recognized by their characteristic O—H stretching absorption (Figure 11.7). Both the position of this absorption and its intensity depend on the extent of hydrogen bonding (Section 8.1C). Under normal conditions, where there is extensive hydrogen bonding between alcohol molecules, O—H stretching occurs as a broad peak at 3200–3500 cm^{-1}. The C—O stretching vibration of alcohols appears in the range 1050–1250 cm^{-1}.

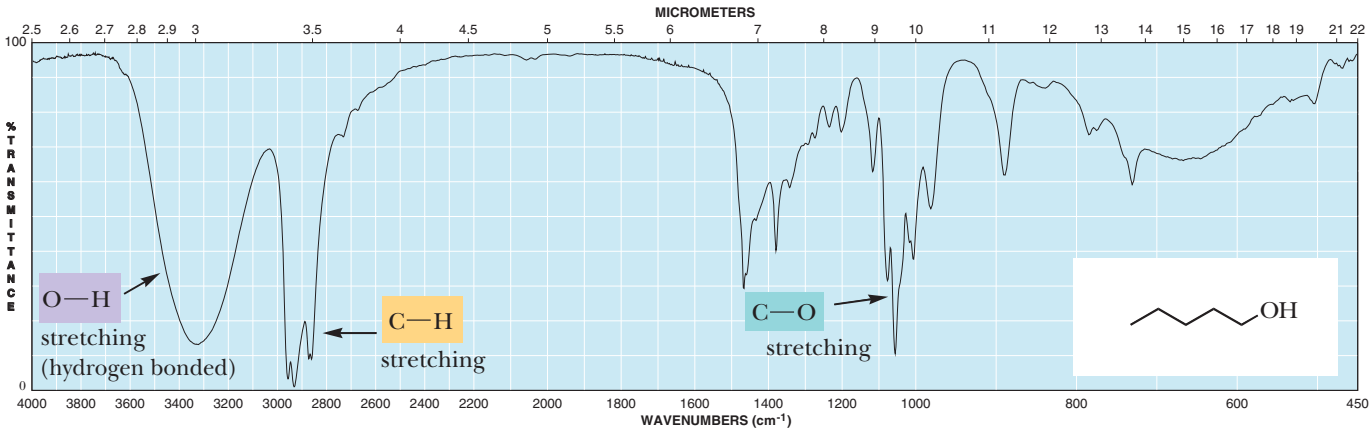


FIGURE 11.7 Infrared spectrum of 1-pentanol.

C. Ethers

The C—O stretching frequencies of ethers are similar to those observed in alcohols and esters (1070 and 1150 cm^{-1}). The presence or absence of O—H stretching at 3200–3500 cm^{-1} for a hydrogen-bonded O—H can be used to distinguish between an ether and an alcohol. The C—O stretching vibration is also present in esters. In this case, we can use the presence or absence of C═O stretching to distinguish between an ether and an ester. Figure 11.8 shows an infrared spectrum of diethyl ether. Notice the absence of O—H stretching.

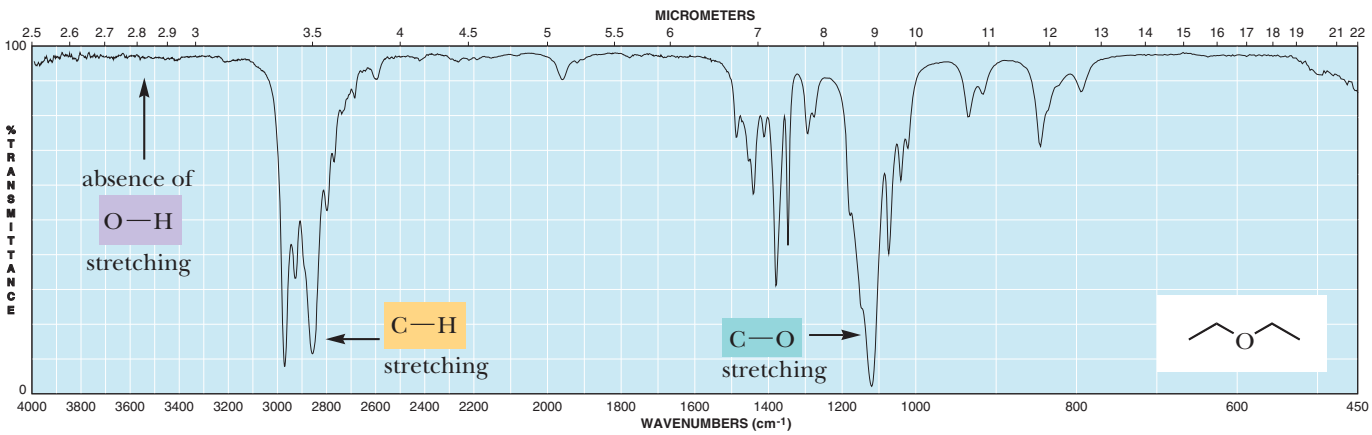


FIGURE 11.8 Infrared spectrum of diethyl ether.

D. Amines

The most important and readily observed infrared absorptions of primary and secondary amines are due to N—H stretching vibrations and appear in the region from 3100 to 3500 cm^{-1}. Primary amines have two peaks in this region, one caused by a symmetric stretching vibration and the other by asymmetric stretching. The two N—H stretching absorptions

characteristic of a primary amine can be seen in the IR spectrum of butanamine (Figure 11.9). Secondary amines give only one absorption in this region. Tertiary amines have no N—H and therefore are transparent in this region of the infrared spectrum.

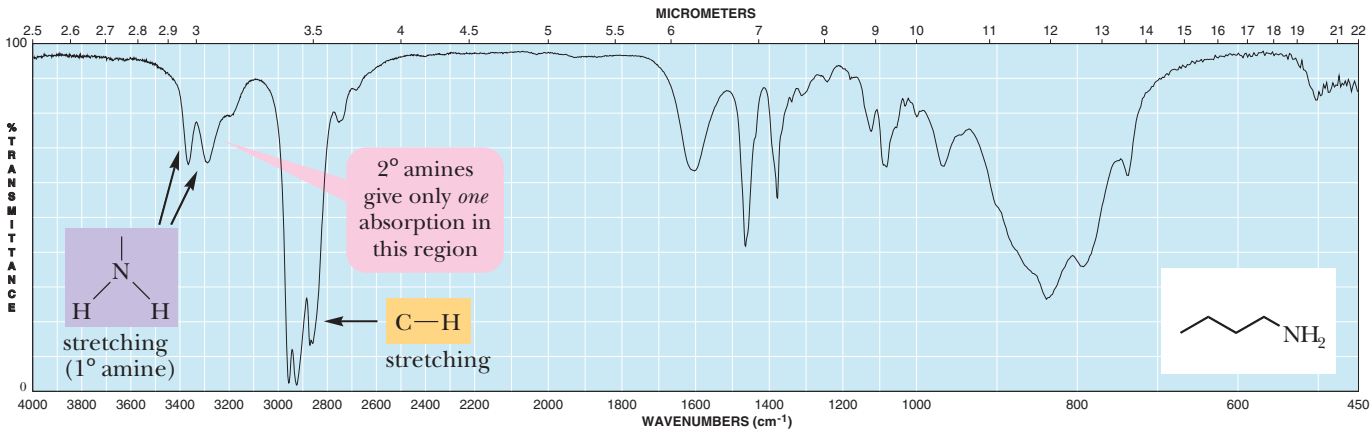


FIGURE 11.9 Infrared spectrum of butanamine, a primary amine.

E. Aldehydes and Ketones

Aldehydes and ketones (Section 1.7C) show characteristic strong infrared absorption between 1705 and 1780 cm^{-1} associated with the stretching vibration of the carbon–oxygen double bond. The stretching vibration for the carbonyl group of menthone occurs at 1705 cm^{-1} (Figure 11.10).

Because several different functional groups contain a carbonyl group, it is often not possible to tell from absorption in this region alone whether the carbonyl-containing compound is an aldehyde, a ketone, a carboxylic acid, or an ester.

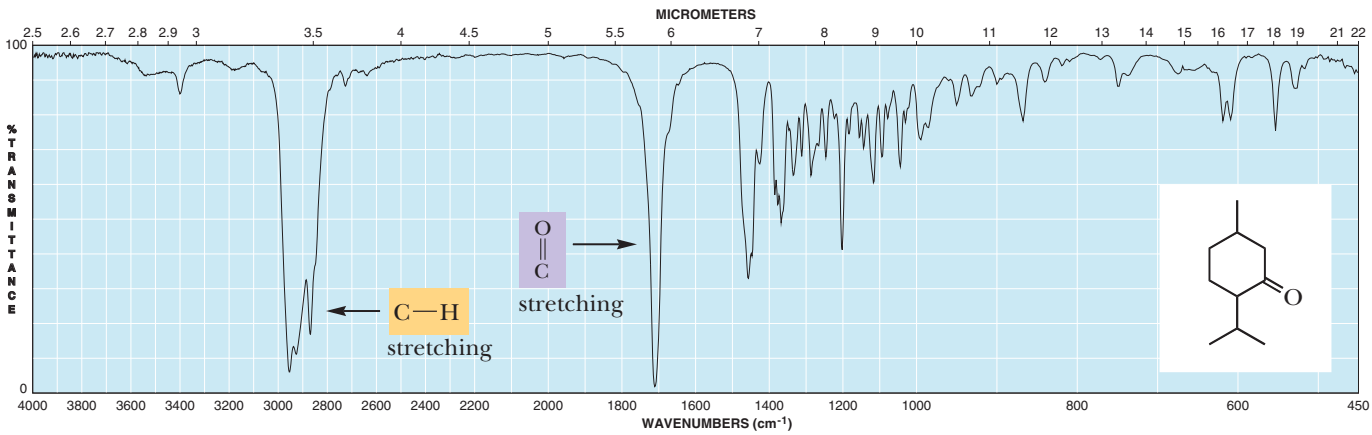


FIGURE 11.10 Infrared spectrum of menthone.

F. Carboxylic Acids and Their Derivatives

The carboxyl group of a carboxylic acid gives rise to two characteristic absorptions in the infrared spectrum. One of these occurs in the region from 1700 to 1725 cm^{-1} and is associated with the stretching vibration of the carbonyl group. This region is essentially the same as that for the absorption of the carbonyl groups of aldehydes and ketones. The other infrared absorption characteristic of a carboxyl group is a peak between 2400 and 3400 cm^{-1} due to the stretching vibration of the O—H group. This peak, which often overlaps the C—H stretching absorptions, is generally very broad due to hydrogen bonding between molecules of the carboxylic acid. Both C═O and O—H stretchings can be seen in the infrared spectrum of butanoic acid, shown in Figure 11.11.

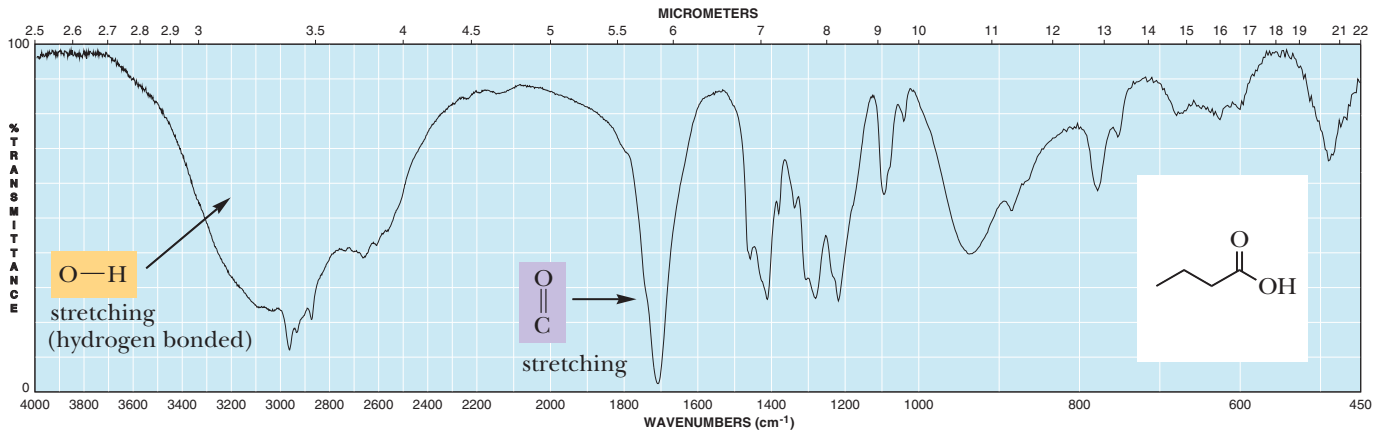


FIGURE 11.11 Infrared spectrum of butanoic acid.

Esters display strong C═O stretching absorption in the region between 1735 and 1800 cm^{-1}. In addition, they display strong C—O stretching absorption in the region from 1000 to 1250 cm^{-1} (Figure 11.12).

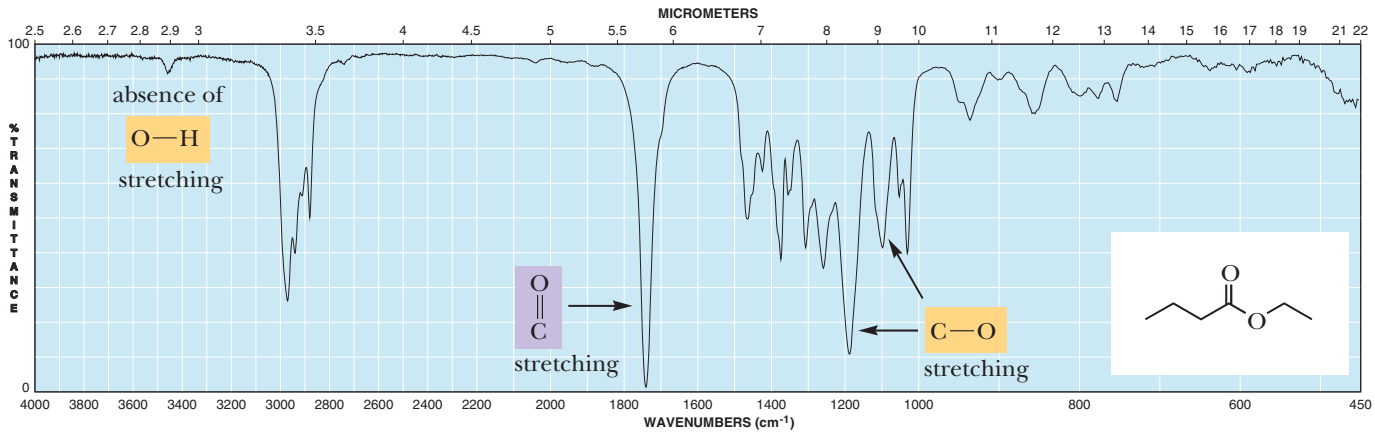
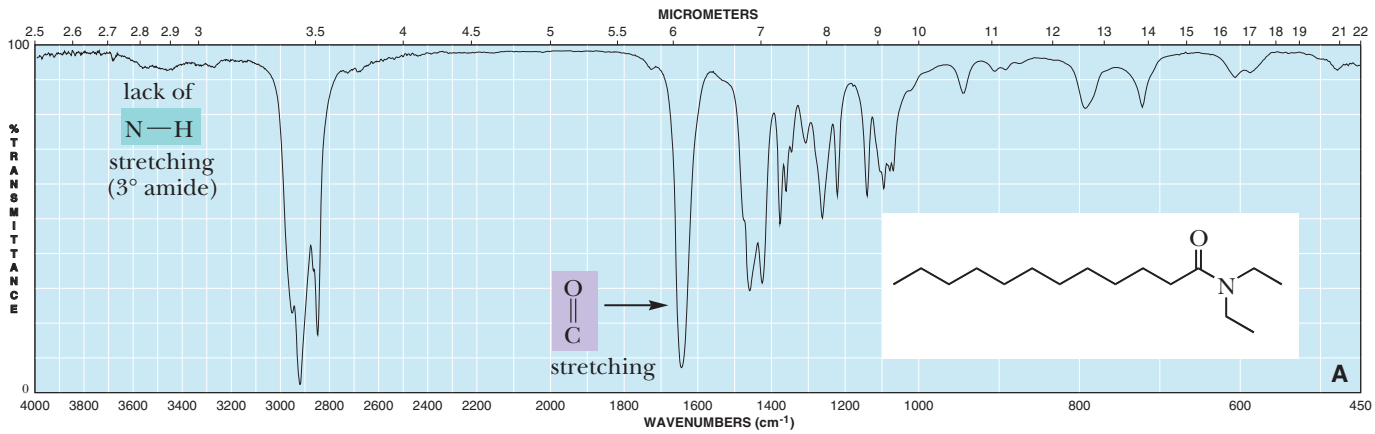


FIGURE 11.12 Infrared spectrum of ethyl butanoate.

The carbonyl stretching of amides occurs at 1630–1680 cm^{-1}, a lower series of wavenumbers than for other carbonyl compounds. Primary and secondary amides show N—H stretching in the region from 3200 to 3400 cm^{-1}; primary amides ($RCONH_2$) show two N—H absorptions, whereas secondary amides (RCONHR) show only a single N—H absorption. Tertiary amides, of course, do not show N—H stretching absorptions. See the three spectra in Figure 11.13.



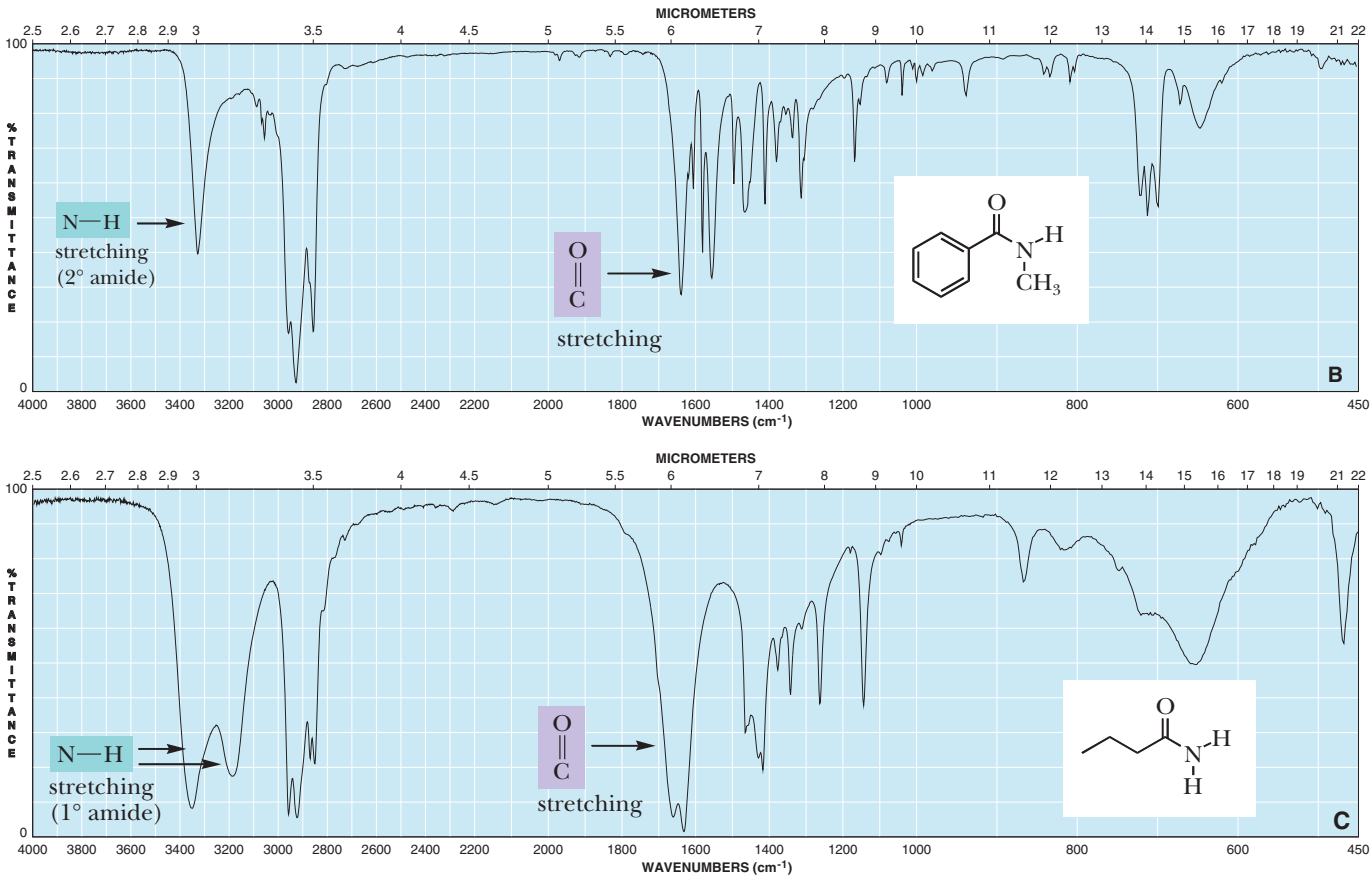
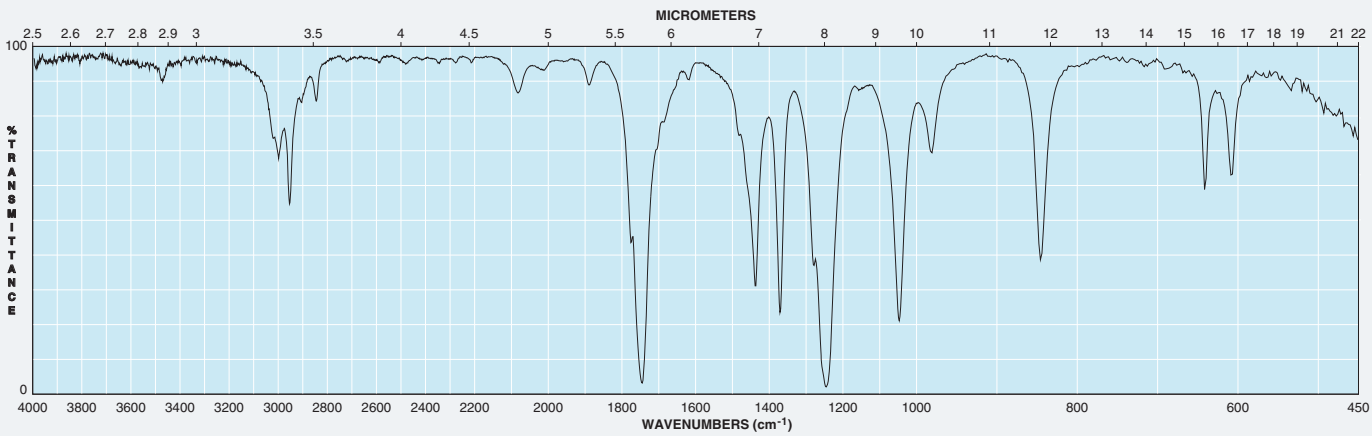


FIGURE 11.13 Infrared spectra of *N,N*-diethyldodecanamide (**A**, a tertiary amide), *N*-methylbenzamide (**B**, a secondary amide), butanamide (**C**, a primary amide).

EXAMPLE 11.4

An unknown compound with the molecular formula $C_3H_6O_2$ yields the following IR spectrum. Draw possible structures for the unknown.



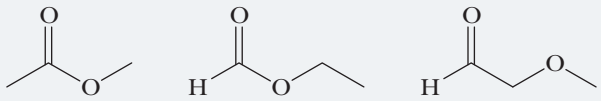
STRATEGY

Start at 4000 cm^{-1} and move down the wavenumber scale. Make note of characteristic peaks, especially those that are unique to certain functional groups. Observe that the absence of peaks also provides clues for the types of functional groups that cannot be present. Once all the possible functional groups have been identified, propose chemical structures using these functional groups and the elements provided by the molecular formula. In Section 11.4G, we learn the concept of index of hydrogen deficiency, which can also be used in these types of problems to determine the structure of an unknown compound.

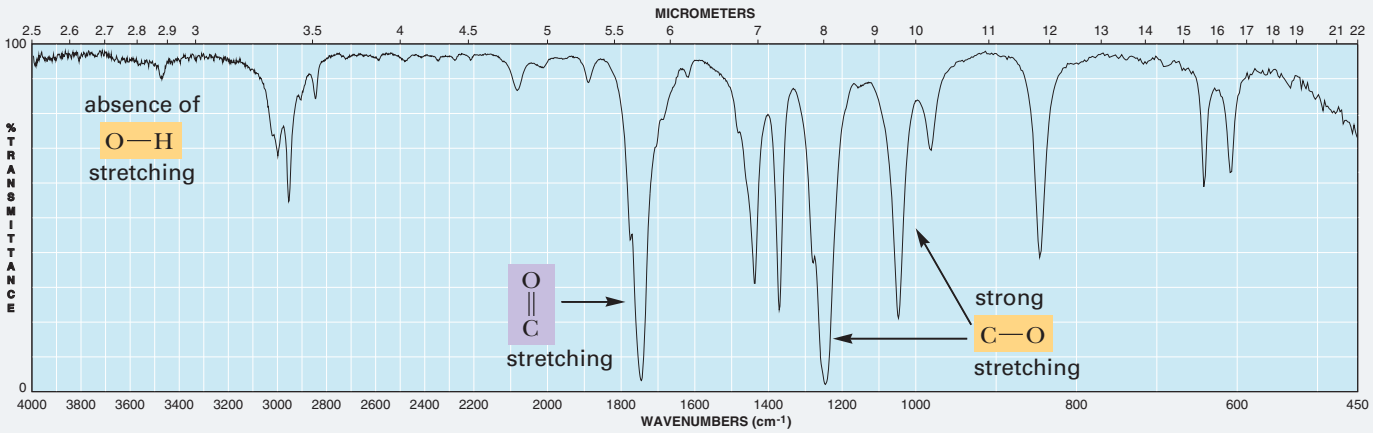
SOLUTION

The IR spectrum shows a strong absorption at approximately 1750 cm^{-1}, which is indicative of a C═O group. The spectrum also shows strong C—O absorption peaks at 1250 and 1050 cm^{-1}. Furthermore, there are no peaks above 3100 cm^{-1},

which eliminates the possibility of an O—H group. On the basis of these data, three structures are possible for the given molecular formula:



The spectrum can now be annotated as follows:



See problems 11.22–11.28

PROBLEM 11.4

What does the value of the wavenumber of the stretching frequency for a particular functional group indicate about the relative strength of the bond in that functional group?

Chemical Connections 11B

INFRARED SPECTROSCOPY: A WINDOW ON CLIMATE CHANGE

Using data from infrared spectroscopy, scientists can calculate the global warming potential (GWP) for scores of halocarbons and related compounds, some of which are given in the table below. In Chapter 7, we learned that the replacement of a halogen with a hydrogen makes a halocarbon more chemically reactive in the atmosphere (Chemical Connections 7A). This has resulted in the development of hydrofluorocarbons (HFC) and hydrofluoroolefins (HFO) as replacements for chlorofluorocarbons (CFC, or Freons®). Among them, HFO-12334yf has the lowest lifetime in the atmosphere as well as the lowest GWP. As a result, HFO-12334yf has become the environmentally friendly refrigerant gas of choice for home and commercial cooling systems.

Global Warming Potential for Some Refrigerant Gases

Compound	Formula	Atmospheric Lifetime (years)	20-year Global Warming Potential	
CFC-11	CCl_3F	45	6,730	Chlorofluorocarbons (Freons)
CFC-12	CCl_2F_2	100	11,000	
CFC-113	CCl_2FCClF_2	85	6,540	
HFC-32	CH_2F_2	4.9	2,330	Hydrofluorocarbons
HFC-152a	CH_3CHF_2	1.4	437	
HFO-1234yf	$CF_3CF{=}CH_2$	0.03	< 1	
Methane	CH_4	12.4	72	Natural gas

Values of GWP are relative to CO_2, which has a value of 1.

Question

Besides atmospheric lifetime and GWP, what other factor(s) might affect a compound's potential harm to the atmosphere?

G. Index of Hydrogen Deficiency

We can obtain valuable information about the structural formula of an unknown compound by inspecting its molecular formula. In addition to learning the number of atoms of carbon, hydrogen, oxygen, nitrogen, and so forth in a molecule of the compound, we can determine what is called its **index of hydrogen deficiency (IHD)**, which is the sum of the number of rings and pi bonds in a molecule. We determine this quantity by comparing the number of hydrogens in the molecular formula of a compound of unknown structure with the number of hydrogens in a **reference compound** with the same number of carbon atoms and with no rings or pi bonds. The molecular formula of a reference hydrocarbon is C_nH_{2n+2} (Section 3.1).

Index of hydrogen deficiency (IHD) The sum of the number of rings and pi bonds in a molecule.

$$\text{IHD} = \frac{(\text{H}_{\text{reference}} - \text{H}_{\text{molecule}})}{2}$$

EXAMPLE 11.5

Calculate the IHD for 1-hexene, with the molecular formula C_6H_{12}, and account for this deficiency by reference to the structural formula of cyclohexene.

STRATEGY

Determine the number of hydrogens in the reference compound; then use the formula

$$\text{IHD} = \frac{(\text{H}_{\text{reference}} - \text{H}_{\text{molecule}})}{2}.$$

SOLUTION

The molecular formula of the reference hydrocarbon with six carbon atoms is C_6H_{14}. The IHD of 1-hexene is $(14-12)/2 = 1$ and is accounted for by the one pi bond in 1-hexene.

See problems 11.21–11.28

PROBLEM 11.5

Calculate the IHD of cyclohexene, C_6H_{10}, and account for this deficiency by reference to the structural formula of the compound.

To determine the molecular formula of a reference compound containing elements besides carbon and hydrogen, write the formula of the reference hydrocarbon, add to it other elements contained in the unknown compound, and make the following adjustments to the number of hydrogen atoms:

1. For each atom of a monovalent Group 7 element (F, Cl, Br, I) added to the reference hydrocarbon, subtract one hydrogen; halogen substitutes for hydrogen and reduces the number of hydrogens by one per halogen. The general formula of an acyclic monochloroalkane, for example, is $C_nH_{2n+1}Cl$.
2. No correction is necessary for the addition of atoms of Group 6 elements (O, S, Se) to the reference hydrocarbon. Inserting a divalent Group 6 element into a reference hydrocarbon does not change the number of hydrogens.
3. For each atom of a trivalent Group 5 element (N and P) added to the formula of the reference hydrocarbon, add one hydrogen. Inserting a trivalent Group 5 element adds one hydrogen to the molecular formula of the reference compound. The general molecular formula for an acyclic alkylamine, for example, is $C_nH_{2n+3}N$.

EXAMPLE 11.6

Isopentyl acetate, a compound with a bananalike odor, is a component of the alarm pheromone of honeybees. The molecular formula of isopentyl acetate is $C_7H_{14}O_2$. Calculate the IHD of this compound.

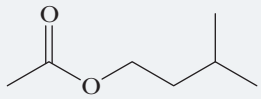
STRATEGY

Determine the number of hydrogens in the reference compound and then use the formula

$$\text{IHD} = \frac{(\text{H}_{\text{reference}} - \text{H}_{\text{molecule}})}{2}.$$

SOLUTION

The molecular formula of the reference hydrocarbon is C_7H_{16}. Adding oxygens to this formula does not require any correction in the number of hydrogens. The molecular formula of the reference compound is $C_7H_{16}O_2$, and the IHD is $(16-14)/2 = 1$, indicating either one ring or one pi bond. Following is the structural formula of isopentyl acetate, which contains one pi bond, in this case in the carbon–oxygen double bond:

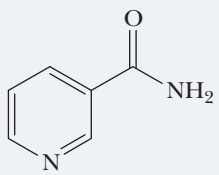


Isopentyl acetate

See problems 11.21–11.28

PROBLEM 11.6

The IHD of niacin is 5. Account for this value by reference to the structural formula of niacin.



Nicotinamide
(Niacin)

HOW TO 11.1 Approach Infrared Spectroscopy Structure Determination Problems

It is useful to develop a systematic approach to problems that ask you to determine a structure given a molecular formula and an infrared spectrum. Following are some guidelines for tackling such problems.

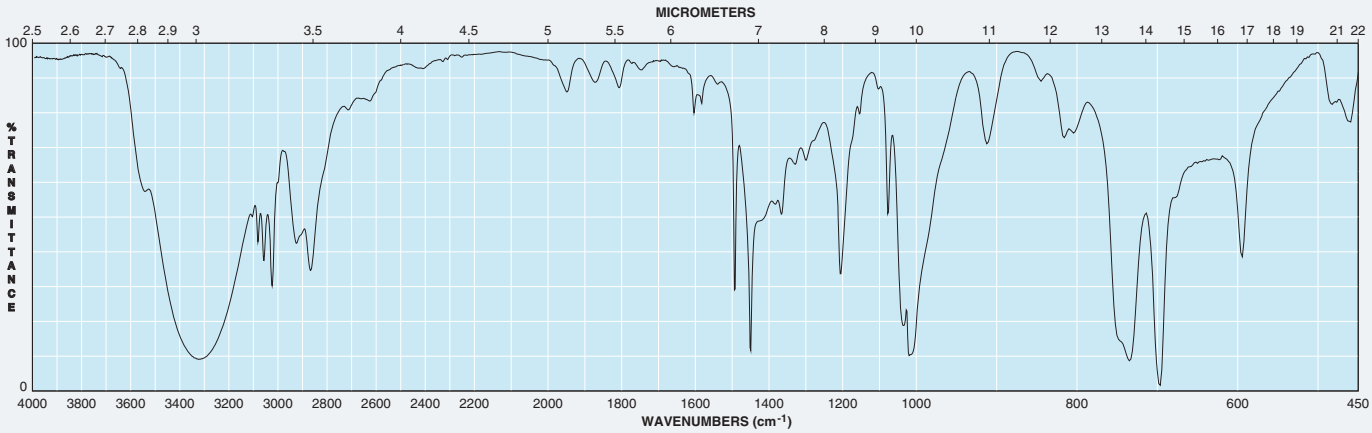
(a) *Determine the IHD.* Knowing the potential number of rings, double bonds, or triple bonds in an unknown compound is of great assistance in solving the structure. For example, if IHD = 1, you know that the unknown can have either a ring or a double bond, but not both. It also cannot have a triple bond because that would require an IHD = 2.

(b) *Move from left to right to identify functional groups in the IR spectrum.* Because the types of transitions in an IR spectrum become less specific as absorptions approach and go lower than 1000 cm^{-1}, it is most useful to start on the left side of an IR spectrum. The shorter the bond, the higher in wavenumber its absorption. This is why O—H, N—H, and C—H bond vibrations occur above 3900 cm^{-1}. Proceeding to the right, we then encounter C—C triple bond stretching vibrations. C═O bonds are shorter than C═C bonds and therefore occur at higher wavenumbers (1800–1650 cm^{-1}) than C═C bonds (1680–1600 cm^{-1}).

(c) *Draw possible structures and verify your structures with the data.* Do not try to think of the answer entirely in your mind. Rather, jot down some structures on paper. Once you have one or more possible structures, verify that these possibilities work with the IHD value and the functional groups indicated by the IR spectrum. Usually, incorrect structures will obviously conflict with one or more of these data items.

EXAMPLE 11.7

Determine possible structures for a compound that yields the following IR spectrum and has a molecular formula of C_7H_8O:

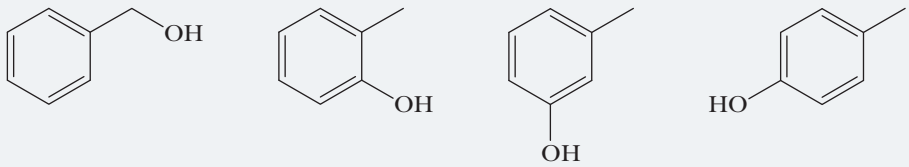


STRATEGY

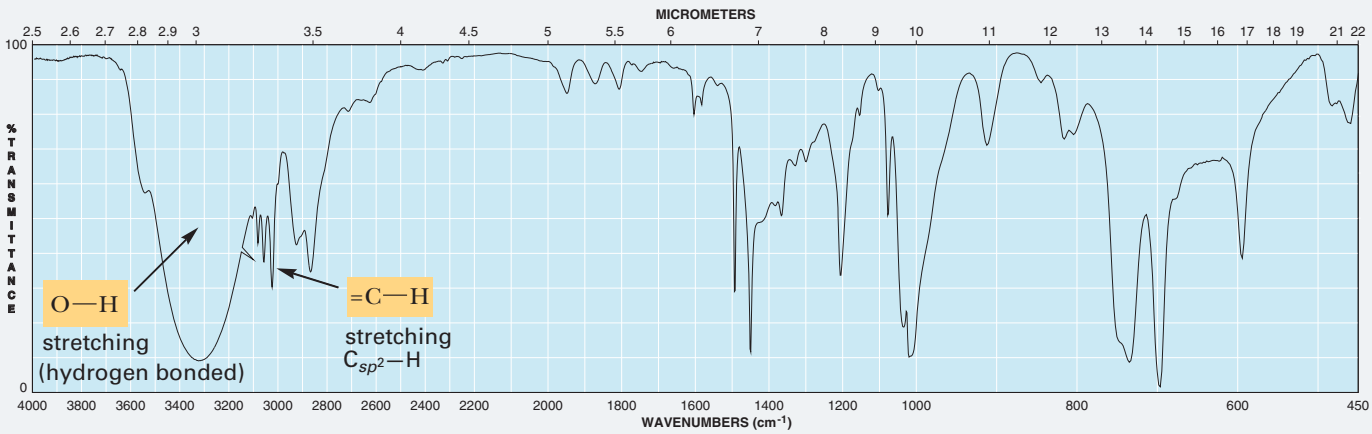
Determine the IHD and use this value as a guide to the combination of rings, double bonds, or triple bonds possible in the unknown. Analyze the IR spectrum, starting at 4000 cm^{-1} and moving down the wavenumber scale. Make note of characteristic peaks, especially those that are unique to certain functional groups. Note that the absence of peaks also provides clues for the types of functional groups that cannot be present. Once all the possible functional groups have been identified, propose chemical structures using these functional groups and the elements provided by the molecular formula.

SOLUTION

The IHD for C_7H_8O is 4, based on the reference formula C_7H_{16}. We can exclude C—C triple bonds because of the absence of a peak from the triple bond C—C stretch (2100–2260 cm^{-1}) and the absence of a terminal alkyne C—H stretch (3300 cm^{-1}). We see C—C double bond C—H stretching peaks just above 3000 cm^{-1}. However, we don't see C—C double bond stretching between 1600 and 1680 cm^{-1}. Recall that aromatic hydrocarbons do not exhibit the same chemical properties as alkenes, so an arene ring remains a possibility. Benzene, with 3 double bonds and a ring, would have an IHD of 4 (this is a common functional group to keep in mind whenever we encounter an IHD of 4 or more). By considering a benzene ring as a possibility, the remaining structural possibilities are limited. Because there is no strong absorption between 1630 and 1800 cm^{-1}, a carbonyl group (C═O) can be excluded. The last piece of evidence is the strong, broad O—H stretching peak at approximately 3310 cm^{-1}. Because we must have an OH group, we cannot propose any structures with an OCH_3 (ether) group. Based on this interpretation of the spectrum, the following four structures are possible:



The given spectrum can now be annotated as follows:



See problems 11.22–11.28

PROBLEM 11.7

Determine possible structures for the same spectrum (above) for a compound with molecular formula $C_8H_{10}O$. What does example 11.7 and this problem tell you about the effectiveness of IR spectroscopy for determining the structure of an unknown compound?

The preceding example illustrates the power and limitations of IR spectroscopy. The power lies in its ability to provide us with information regarding the functional groups in a molecule. IR spectroscopy does not, however, provide us with information on how those functional groups are connected. Fortunately, another type of spectroscopy—nuclear magnetic resonance (NMR) spectroscopy—does provide us with connectivity information.

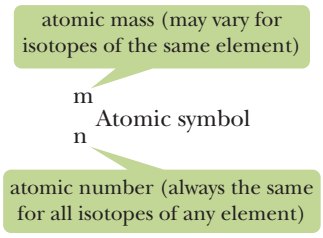
11.5 What Is Nuclear Magnetic Resonance?

The phenomenon of nuclear magnetic resonance was first detected in 1946 by U.S. scientists Felix Bloch and Edward Purcell, who shared the 1952 Nobel Prize for Physics for their discoveries. The particular value of nuclear magnetic resonance (NMR) spectroscopy is that it gives us information about the number and types of atoms in a molecule, for example, about the number and types of hydrogens using **^{1}H-NMR spectroscopy**, and about the number and types of carbons using **^{13}C-NMR spectroscopy**.

From your study of general chemistry, you may already be familiar with the concept that an electron has a **spin** and that a spinning charge creates an associated magnetic field. In effect, an electron behaves as if it is a tiny bar magnet. An atomic nucleus that has an odd mass or an odd atomic number also has a spin and behaves as if it is a tiny bar magnet. Recall that when designating isotopes, a superscript represents the mass of the element.

HOW TO 11.2 Determine Whether an Atomic Nucleus Has a Spin (Behaves as If It Were a Tiny Bar Magnet)

Determine the mass and atomic number of the atom. If *either* is an odd number, the atom will have a spin and behave as a tiny bar magnet.



EXAMPLE 11.8

Which of the following nuclei are capable of behaving like tiny bar magnets?

(a) $^{14}_{6}C$ **(b)** $^{14}_{7}N$

STRATEGY

Any nucleus that has a spin (those that have either an odd mass or an odd atomic number) will act as a tiny bar magnet.

SOLUTION

(b) $^{14}_{6}C$, a radioactive isotope of carbon, has neither an odd mass number nor an odd atomic number and therefore cannot behave as if it were a tiny bar magnet.

(c) $^{14}_{7}N$, the most common naturally occurring isotope of nitrogen (99.63% of all nitrogen atoms), has an odd atomic number and therefore behaves as if it were a tiny bar magnet.

PROBLEM 11.8

Which of the following nuclei are capable of behaving like tiny bar magnets?

(a) $^{31}_{15}P$ **(b)** $^{195}_{78}Pt$

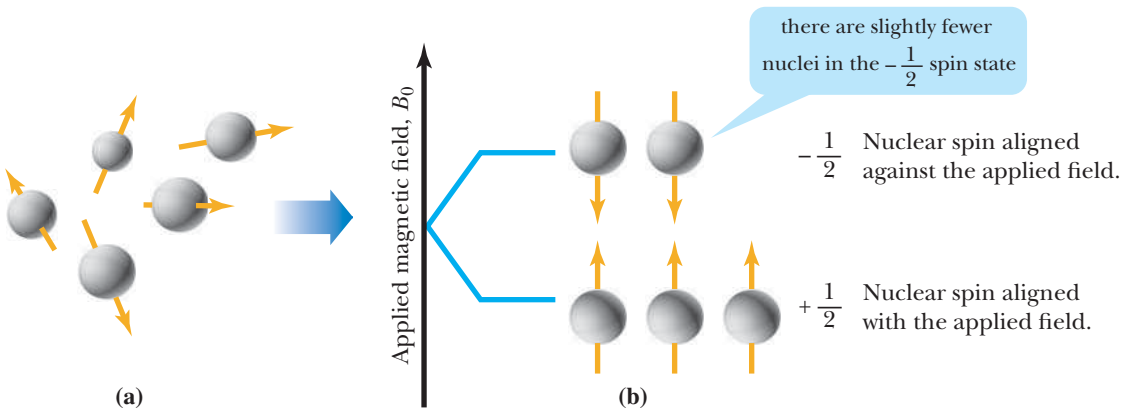


FIGURE 11.14 ^1H and ^{13}C nuclei (a) in the absence of an applied magnetic field and (b) in the presence of an applied field. ^1H and ^{13}C nuclei with spin $+\frac{1}{2}$ are aligned with the applied magnetic field and are in the lower spin energy state; those with spin $-\frac{1}{2}$ are aligned against the applied magnetic field and are in the higher spin energy state.

Within a collection of ^1H and ^{13}C atoms, the spins of their tiny nuclear bar magnets are completely random in orientation. When we place them between the poles of a powerful magnet, however, interactions between their nuclear spins and the **applied magnetic field** are quantized, and only two orientations are allowed (Figure 11.14).

The difference in energy between these nuclear spin states for ^1H is 0.120 J/mol (0.0286 cal/mol), which corresponds to electromagnetic radiation of approximately 300 MHz (300,000,000 Hz). The difference in energy for the two spin states of ^{13}C is 0.035 J/mol (0.0072 cal/mol). Both of these values fall within the radio-frequency range of the electromagnetic spectrum, and irradiation of the nuclei in the lower energy spin state with radio-frequency radiation of the appropriate energy causes them to absorb energy and results in their nuclear spins flipping from the lower energy state to the higher energy state, as illustrated in Figure 11.15. In this context, **resonance** is defined as the absorption of electromagnetic radiation by a spinning nucleus and the resulting flip of its nuclear spin state. The instrument we use to detect this absorption and resulting flip of nuclear spin state records it as a **resonance signal**.

Resonance The absorption of electromagnetic radiation by a spinning nucleus and the resulting "flip" of its spin from a lower energy state to a higher energy state.

Resonance signal A recording of nuclear magnetic resonance in an NMR spectrum.

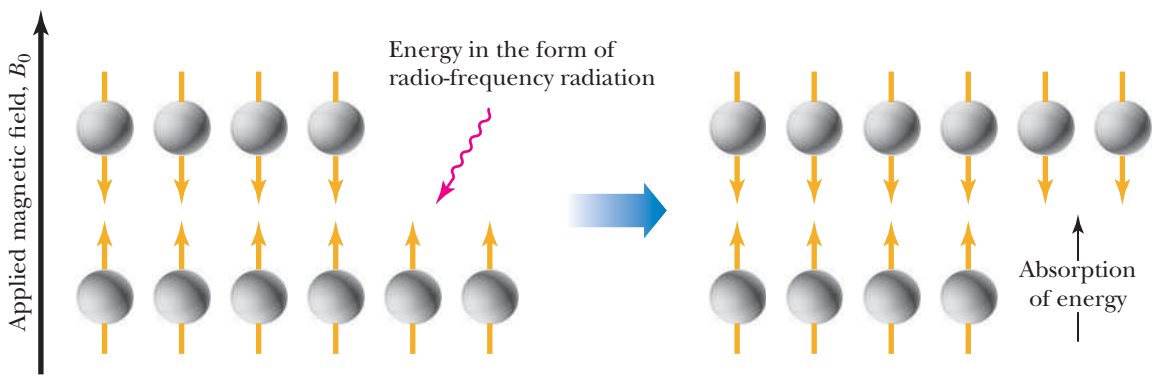


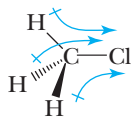
FIGURE 11.15 An example of resonance for nuclei of spin $\frac{1}{2}$.

11.6 What Is Shielding?

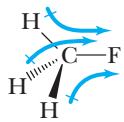
If all ^{1}H nuclei absorbed the same frequency of electromagnetic radiation (i.e., if they all resonated at the same frequency), all hydrogens in a compound would give rise to one and only one NMR signal, and NMR spectroscopy would be an ineffective technique for determining the structure of a molecule. Fortunately, hydrogens in most organic molecules are surrounded by electrons and by other atoms. The electrons that surround a nucleus also have spin and thereby create **local magnetic fields** that oppose the applied field. Although these local magnetic fields created by electrons are orders of magnitude weaker than the applied magnetic fields used in NMR spcctroscopy, they act to shield hydrogens from the applied field. The greater the **shielding** of a particular hydrogen by local magnetic fields, the greater is the strength of the applied field necessary to bring that hydrogen into resonance.

Shielding In NMR spectroscopy, electrons around a nucleus create their own local magnetic fields and thereby shield the nucleus from the applied magnetic field.

As we learned in previous chapters, the electron density around a nucleus can be influenced by the atoms that surround the nucleus. For example, the electron density around the hydrogen atoms in fluoromethane is less than that around the hydrogen atoms in chloromethane, due to the greater electronegativity of fluorine relative to chlorine. Thus, we can say that the hydrogen atoms in chloromethane are *more shielded* than the hydrogen atoms in fluoromethane:



Chlorine is less electronegative than fluorine, resulting in a smaller inductive effect and thereby a greater electron density around each hydrogen. We say that the hydrogens in chloromethane are more **shielded** (by their local environment) than those in fluoromethane.



Fluorine's greater electronegativity produces a larger inductive effect and thereby reduces the electron density around each hydrogen. We say that these hydrogens are **deshielded**.

The differences in resonance frequencies among the various ^{1}H nuclei within a molecule caused by shielding are generally very small. The difference between the resonance frequencies of hydrogens in chloromethane compared with those in fluoromethane, for example, is only 360 Hz under an applied field of 7.05 tesla. Considering that the radio-frequency radiation used at this applied field is approximately 300 MHz (300×10^6 Hz), the difference in resonance frequencies between these two sets of hydrogens is only slightly greater than 1 **part per million** (1 ppm) compared with the irradiating frequency.

$$\frac{360 \text{ Hz}}{300 \times 10^6 \text{ Hz}} = \frac{1.2}{10^6} = 1.2 \text{ ppm}$$

NMR spectrometers are able to detect these small differences in resonance frequencies. The importance of shielding for elucidating the structure of a moleculc will be discussed in Section 11.10.

11.7 What Is a ^{1}H-NMR Spectrum?

Resonance of nuclei is achieved in an NMR spectrometer (Figure 11.16), which consists of a powerful magnet, a radio-frequency generator, a radio-frequency detector, and a sample chamber. Analysis of a sample produces a ^{1}H-NMR spectrum (Figure 11.17), which consists of a horizontal axis representing the **delta (δ) scale**, with values from 0 on the right to 10 on the left, and a vertical axis representing the intensity of the resonance signal.

It is customary to measure the resonance frequencies of individual nuclei relative to the resonance frequency of the same nuclei in a reference compound. The reference

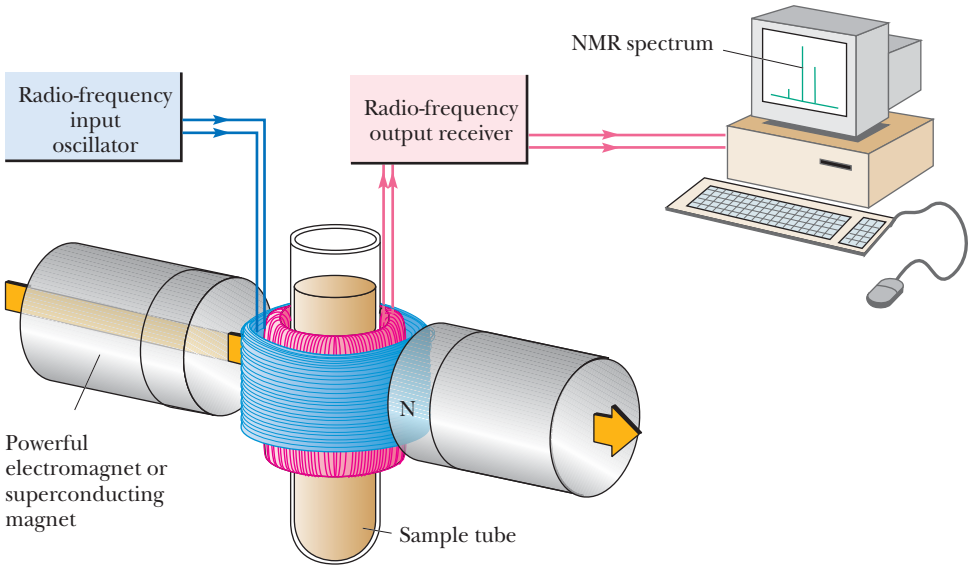
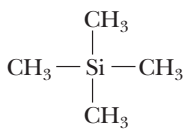


FIGURE 11.16 Schematic diagram of a nuclear magnetic resonance spectrometer.

compound now universally accepted for ^{1}H-NMR and ^{13}C-NMR spectroscopy is **tetramethylsilane (TMS)** because it is relatively unreactive and its hydrogen and carbon atoms are highly shielded due to the less electronegative silicon atom. The latter fact ensures that most other resonance signals will be less shielded than the signal for TMS.



Tetramethylsilane (TMS)

When we determine a ^{1}H-NMR spectrum of a compound, we report how far the resonance signals of its hydrogens are shifted from the resonance signal of the hydrogens in TMS. When we determine a ^{13}C-NMR spectrum, we report how far the resonance signals of its carbons are shifted from the resonance signal of the four carbons in TMS.

Chemical shift (δ) The position of a signal on an NMR spectrum relative to the signal of tetramethylsilane (TMS); expressed in delta (δ) units, where 1 δ equals 1 ppm.

To standardize reporting of NMR data, workers have adopted a quantity called the **chemical shift (δ)**. Chemical shift is calculated by dividing the shift in frequency of a signal (relative to that of TMS) by the operating frequency of the spectrometer. Because NMR spectrometers operate at MHz frequencies (i.e., millions of Hz), we express the chemical

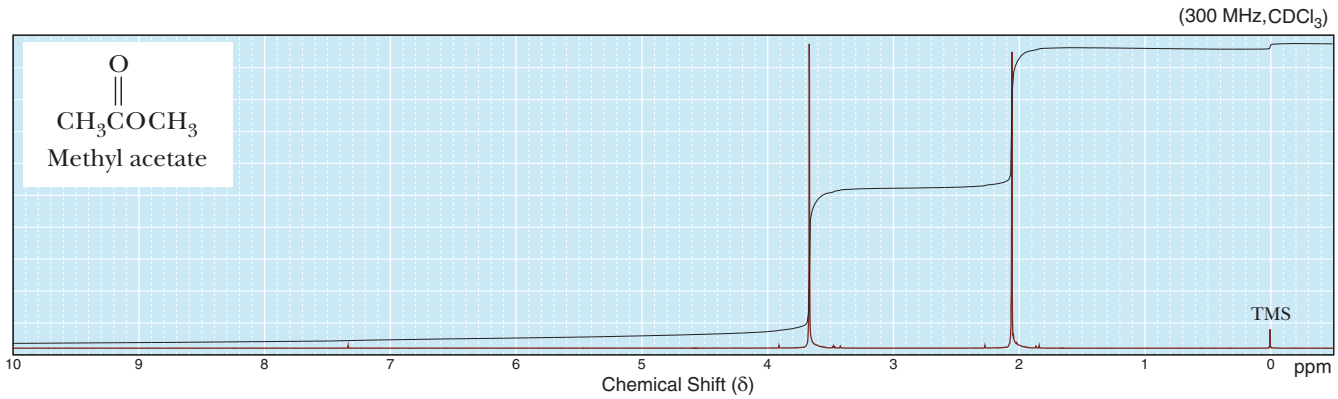


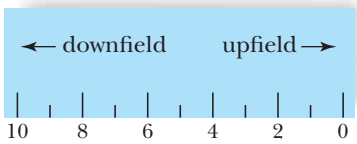
FIGURE 11.17 ^{1}H-NMR spectrum of methyl acetate.

shift in parts per million. A sample calculation is provided for the signal at 2.05 ppm in the ^{1}H-NMR spectrum for methyl acetate (Figure 11.17), a compound used in the manufacture of artificial leather.

$$\delta = \frac{\text{Shift in frequency of a signal from TMS (Hz)}}{\text{Operating frequency of the spectrometer (Hz)}}$$

the hydrogens on this methyl group cause a signal to occur 615 Hz from the TMS signal in a 300 MHz NMR spectrometer

e.g., $CH_3C(=O)OCH_3$ $\quad \dfrac{615 \text{ Hz}}{300 \times 10^6 \text{ Hz}} = \dfrac{2.05 \text{ Hz}}{\text{million Hz}} = 2.05$ parts per million (ppm)



The small signal at δ 0 in this spectrum represents the hydrogens of the reference compound, TMS. The remainder of the spectrum consists of two signals: one for the hydrogens of the $-OCH_3$ group and one for the hydrogens of the methyl bonded to the carbonyl group. It is not our purpose at the moment to determine why each set of hydrogens gives rise to its respective signal, but only to recognize the form in which we record an NMR spectrum and to understand the meaning of the calibration marks.

A note on terminology. If a signal is shifted toward the left on the chart paper, we say that it is shifted **downfield**, meaning that nuclei giving rise to that signal are less shielded and come into resonance at a weaker applied field. Conversely, if a signal is shifted toward the right of the spectrum, we say that it is shifted **upfield**, meaning that nuclei giving rise to that signal are more shielded and come into resonance at a stronger applied field.

Downfield A term used to refer to the relative position of a signal on an NMR spectrum. Downfield indicates a peak to the left of the spectrum (a weaker applied field).

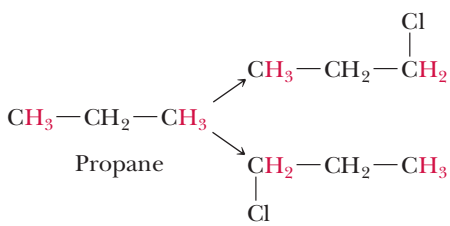
Upfield A term used to refer to the relative position of a signal on an NMR spectrum. Upfield indicates a peak to the right of the spectrum (a stronger applied field).

Equivalent hydrogens Hydrogens that have the same chemical environment.

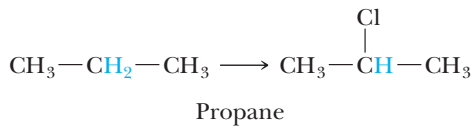
11.8 How Many Resonance Signals Will a Compound Yield in Its ^{1}H-NMR Spectrum?

Given the structural formula of a compound, how do we know how many signals to expect? The answer is that **equivalent hydrogens** give the same ^{1}H-NMR signal; conversely, non-equivalent hydrogens give different ^{1}H-NMR signals. A direct way to determine which hydrogens in a molecule are equivalent is to replace each in turn by a test atom, such as a halogen atom. Two hydrogens treated in this way are equivalent if their "substituted" versions are the same compound or if they are enantiomers of each other. If replacement gives compounds that are different and not enantiomers, the two hydrogens are nonequivalent.

Using this substitution test, we can show that propane contains two sets of equivalent hydrogens: a set of six equivalent 1° hydrogens and a set of two equivalent 2° hydrogens. Thus we would expect to see two signals, one for the six equivalent $-CH_3$ hydrogens and one for the two equivalent $-CH_2-$ hydrogens:



Replacement of any of the red hydrogens by chlorine gives 1-chloropropane; thus, all the red hydrogens are **equivalent**.

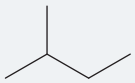


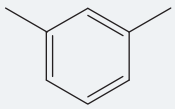
Replacement of either of the blue hydrogens by chlorine gives 2-chloropropane; thus, both of the blue hydrogens are **equivalent**.

EXAMPLE 11.9

State the number of sets of equivalent hydrogens in each compound and the number of hydrogens in each set:

(a) 
2-Methylpropane

(b) 
2-Methylbutane

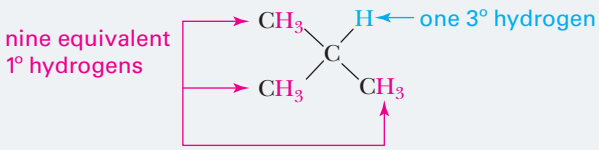
(c) 
m-Xylene

STRATEGY

A reliable way to determine whether hydrogens are equivalent is to replace each with a halogen and name the resulting compound. Hydrogens are equivalent if the two molecules containing their replacements are the same compound or are enantiomers.

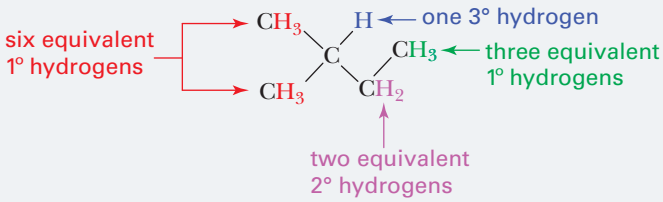
SOLUTION

(a) 2-Methylpropane contains two sets of equivalent hydrogens—a set of nine equivalent 1° hydrogens and one 3° hydrogen:



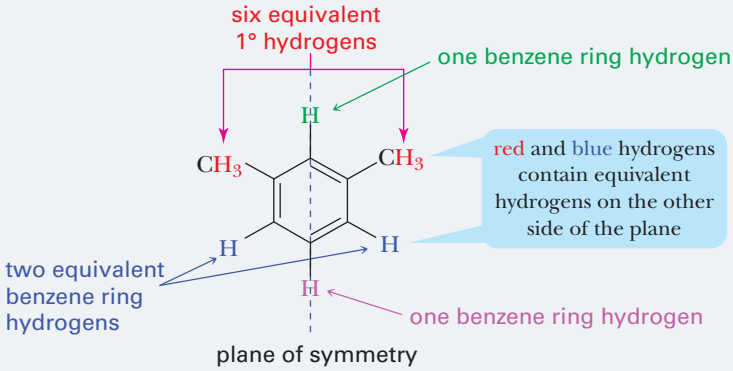
Replacing any one of the red hydrogens with a chlorine yields 1-chloro-2-methylpropane. Replacing the blue hydrogen with a chlorine yields 2-chloro-2-methylpropane.

(b) 2-Methylbutane contains four sets of equivalent hydrogens—two different sets of 1° hydrogens, one set of 2° hydrogens, and one 3° hydrogen:



Replacing any one of the red hydrogens with a chlorine yields 1-chloro-2-methylbutane. Replacing the blue hydrogen with a chlorine yields 2-chloro-2-methylbutane. Replacing a purple hydrogen with a chlorine yields 2-chloro-3-methylbutane. Replacing a green hydrogen with chlorine yields 1-chloro-3-methylbutane.

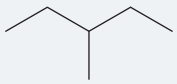
(c) *m*-Xylene contains four sets of equivalent hydrogens—one set of methyl group hydrogens, one set of hydrogens on the benzene ring *ortho* to one methyl group, one hydrogen on the benzene ring *ortho* to both methyl groups, and one hydrogen on the benzene ring *meta* to both methyl groups. In this solution, symmetry is used to illustrate equivalency.



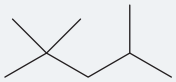
See problem 11.32

PROBLEM 11.9

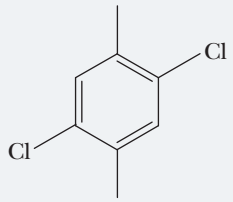
State the number of sets of equivalent hydrogens in each compound and the number of hydrogens in each set:

(a) 

3-Methylpentane

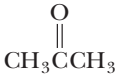
(b) 

2,2,4-Trimethylpentane

(c) 

2,5-Dichloro-4-methyltoluene

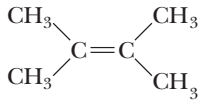
Symmetrical compounds tend to contain a higher amount of equivalent hydrogens, and thus fewer resonance signals in their ^{1}H-NMR spectra. Here are four symmetrical organic compounds, each of which has one set of equivalent hydrogens and gives one signal in its ^{1}H-NMR spectrum:



Propanone (Acetone)

1,2-Dichloroethane

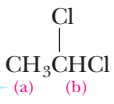
Cyclopentane



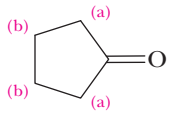
2,3-Dimethyl-2-butene

Molecules with two or more sets of equivalent hydrogens give rise to a different resonance signal for each set. 1,1-Dichloroethane, for example, has three equivalent 1° hydrogens (a) and one 2° hydrogen (b); there are two resonance signals in its ^{1}H-NMR spectrum.

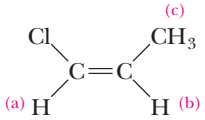
each letter represents a signal in the ^{1}H-NMR spectrum



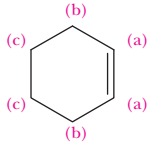
1,1-Dichloroethane
(2 signals)



Cyclopentanone
(2 signals)



(*Z*)-1-Chloropropene
(3 signals)

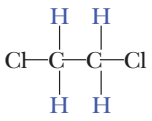


Cyclohexene
(3 signals)

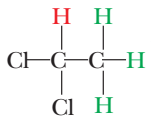
Notice how, by simply counting signals, you can distinguish between the constitutional isomers of 1,2-dichloroethane and 1,1-dichloroethane.

Isomers of $C_2H_4Cl_2$

a ^{1}H-NMR spectrum of this isomer would show only one signal



1,2-Dichloroethane



1,1-Dichloroethane

a ^{1}H-NMR spectrum of this isomer would show two signals

EXAMPLE 11.10

Each of the following compounds gives only one signal in its ^{1}H-NMR spectrum. Propose a structural formula for each.

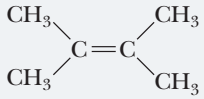
(a) C_2H_6O **(b)** $C_3H_6Cl_2$ **(c)** C_6H_{12}

STRATEGY

Use IHD and the number of signals in a ^{1}H-NMR spectrum to guide your choice of structure. A compound that yields fewer signals than it has hydrogen atoms indicates symmetry in the molecule.

SOLUTION

Following are structural formulas for each of the given compounds. Notice that, for each structure, the replacement of any hydrogen with a chlorine will yield the same compound regardless of the hydrogen being replaced.

(a) CH_3OCH_3 **(b)** CH_3CCH_3 (Cl above and below the central C) **(c)**  or 

PROBLEM 11.10

Each of the following compounds gives only one signal in its ^{1}H-NMR spectrum. Propose a structural formula for each compound.

(a) C_3H_6O **(b)** C_5H_{10} **(c)** C_5H_{12} **(d)** $C_4H_6Cl_4$

11.9 What Is Signal Integration?

We have just seen that the number of signals in a ^{1}H-NMR spectrum gives us information about the number of sets of equivalent hydrogens. Signal areas in a ^{1}H-NMR spectrum can be measured by a mathematical technique called *integration*. In the spectra shown in this text, this information is displayed in the form of a **line of integration** superposed on the original spectrum. The vertical rise of the line of integration over each signal is proportional to the area under that signal, which, in turn, is proportional to the number of hydrogens giving rise to the signal.

Figure 11.18 shows an integrated ^{1}H-NMR spectrum of the gasoline additive *tert*-butyl acetate ($C_6H_{12}O_2$). The spectrum shows signals at δ 1.44 and 1.95. The integrated height of the upfield (to the right) signal is nearly three times as tall as the height of the downfield (to the left) signal (the heights can be accurately determined by assuming that the distance between horizontal grid lines is 10 units). This relationship corresponds to an **integration ratio** of 3:1. We know from the molecular formula that there is a total of 12 hydrogens in the molecule. The ratios obtained from the integration lines are consistent with the presence of one set of 9 equivalent hydrogens and one set of 3 equivalent hydrogens. We will often make use of shorthand notation in referring to an NMR spectrum of a molecule. The notation lists the chemical shift of each signal, beginning with the most deshielded signal and followed by the number of hydrogens that give rise to each signal (based on the integration). The shorthand notation describing the spectrum of *tert*-butyl acetate (Figure 11.18) would be δ 1.95 (3H) and δ 1.44 (9H).

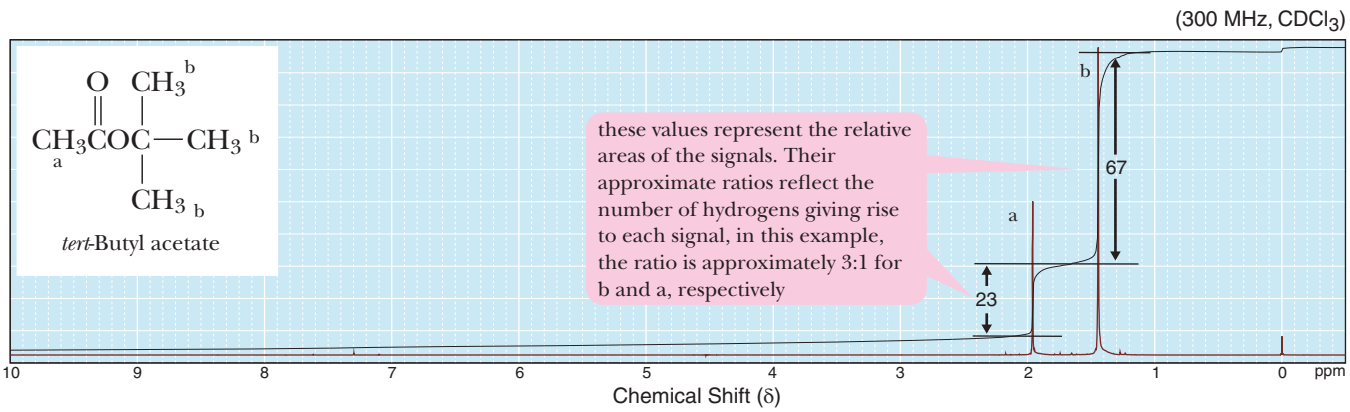


FIGURE 11.18 ^{1}H-NMR spectrum of *tert*-butyl acetate, $C_6H_{12}O_2$, showing a line of integration. The ratio of signal heights for the two peaks is 3:1, which, for a molecule possessing 12 hydrogens, corresponds to 9 equivalent hydrogens of one set and 3 equivalent hydrogens of another set.

EXAMPLE 11.11

Following is a ^{1}H-NMR spectrum for a compound with the molecular formula $C_9H_{10}O_2$. From an analysis of the integration line, calculate the number of hydrogens giving rise to each signal.

STRATEGY

Once the lengths of the integration lines are determined, divide all the numbers by the common denominator to obtain a minimized ratio. For example, if the lengths of the integration lines are 4 : 12 : 8, the minimized ratio becomes (4 : 12 : 8)/4 = 1 : 3 : 2. The minimized ratio values can be treated as the true number of hydrogens if the sum of these numbers is equal to the number of hydrogens from the molecular formula. If the molecular formula contains a greater number of hydrogens than the sum of the ratio values, the ratio values need to be multiplied by some factor to bring their sum to that of the total number of hydrogens. For example, if the minimized ratio is 1 : 3 : 2 and the total number of hydrogens is 12, the ratio must be adjusted by a factor of 2 to be 2 : 6 : 4.

SOLUTION

The ratio of the relative signal heights (obtained from the number of horizontal chart divisions) is 5 : 2 : 3 (from downfield to upfield). The molecular formula indicates that there are 10 hydrogens. Thus, the signal at δ 7.34 represents 5 hydrogens, the signal at δ 5.08 represents 2 hydrogens, and the signal at δ 2.06 represents 3 hydrogens. Consequently, the signals and the number of hydrogens each signal represents are δ 7.34 (5H), δ 5.08 (2H), and δ 2.06 (3H).

PROBLEM 11.11

The line of integration of the two signals in the ^{1}H-NMR spectrum of a ketone with the molecular formula $C_7H_{14}O$ shows a vertical rise of 62 and 10 chart divisions. Calculate the number of hydrogens giving rise to each signal, and propose a structural formula for this ketone.

11.10 What Is Chemical Shift?

The position of a signal along the *x*-axis of an NMR spectrum is known as the **chemical shift** of that signal (Section 11.7). The chemical shift of a signal in a ^{1}H-NMR spectrum can give us valuable information about the type of hydrogens giving rise to that absorption. Hydrogens on methyl groups bonded to sp^3 hybridized carbons, for example, give a signal near δ 0.8–1.0 (compare Figure 11.18). Hydrogens on methyl groups bonded to a carbonyl carbon give signals near δ 2.1–2.3 (compare Figures 11.17 and 11.18), and hydrogens on methyl groups bonded to oxygen give signals near δ 3.7–3.9 (compare Figure 11.17). Table 11.4 lists the average chemical shift for most of the types of hydrogens we deal with in this text.

TABLE 11.4 Average Values of Chemical Shifts of Representative Types of Hydrogens

Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*	Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*
$(CH_3)_4Si$	0 (by definition)	$RCOCH_3$	3.7–3.9
RCH_3	0.8–1.0		
RCH_2R	1.2–1.4	$RCOCH_2R$	4.1–4.7
R_3CH	1.4–1.7		
$R_2C{=}CRCHR_2$	1.6–2.6	RCH_2I	3.1–3.3
$RC{\equiv}CH$	2.0–3.0	RCH_2Br	3.4–3.6
$ArCH_3$	2.2–2.5	RCH_2Cl	3.6–3.8
$ArCH_2R$	2.3–2.8	RCH_2F	4.4–4.5
ROH	0.5–6.0	$ArOH$	4.5–4.7
RCH_2OH	3.4–4.0	$R_2C{=}CH_2$	4.6–5.0
RCH_2OR	3.3–4.0	$R_2C{=}CHR$	5.0–5.7
R_2NH	0.5–5.0	ArH	6.5–8.5
$RCOCH_3$	2.1–2.3	RCH	9.5–10.1
$RCCH_2R$	2.2–2.6	$RCOH$	10–13

*Values are approximate. Other atoms within the molecule may cause the signal to appear outside these ranges.

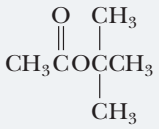
Notice that most of the values shown fall within a rather narrow range from 0 to 13 δ units (ppm). In fact, although the table shows a variety of functional groups and hydrogens bonded to them, we can use the following rules of thumb to remember the chemical shifts of most types of hydrogen:

Chemical Shift (δ)	Type of Hydrogen
0–2	H bonded to an sp^3 carbon.
2–2.8	H bonded to an sp^3 carbon that is at an allylic or benzylic position (i.e., adjacent to a C—C double bond or a benzene ring).
2–4.5	H bonded to an sp^3 carbon that is close to an electronegative element such as N, O, or X. The more electronegative the element, the higher is the chemical shift. Also, the closer the electronegative atom, the higher is the chemical shift.
4.6–5.7	H bonded to an sp^2 carbon in an alkene.
6.5–8.5	H bonded to an sp^2 carbon in an aromatic compound.
9.5–10.1	H bonded to a C=O (an aldehyde hydrogen).
10–13	H of a carboxyl (COOH) group.

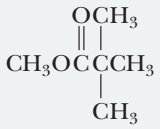
follow these rules of thumb for most ^{1}H-NMR spectra problems

EXAMPLE 11.12

Following are two constitutional isomers with the molecular formula $C_6H_{12}O_2$:



(1)



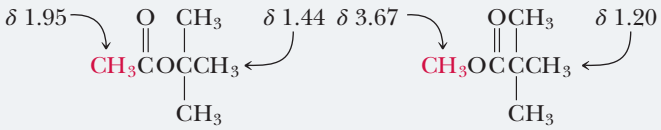
(2)

(a) Predict the number of signals in the ^{1}H-NMR spectrum of each isomer.
(b) Predict the ratio of areas of the signals in each spectrum.
(c) Show how to distinguish between these isomers on the basis of chemical shift.

STRATEGY

This example poses a series of steps that you will repeat often when asked to predict the ^{1}H-NMR spectrum of a compound. First, determine the number of signals by determining the number of equivalent hydrogens (Section 11.8). Then predict the ratio of areas of the signals by counting the number of hydrogens in each equivalent set (if the set of ratios can be reduced further, divide each number by a value that produces whole number ratios). Finally, predict the chemical shift of each set of equivalent hydrogens. If the rules of thumb for predicting chemical shift do not apply, refer to Table 11.4.

SOLUTION



(1) (2)

(a) Each compound contains a set of nine equivalent methyl hydrogens and a set of three equivalent methyl hydrogens.

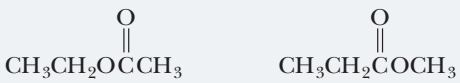
(b) The ^{1}H-NMR spectrum of each consists of two signals in the ratio 9 : 3, or 3 : 1.

(c) The two constitutional isomers can be distinguished by the chemical shift of the single $-CH_3$ group, or in other words, the signal that integrates to 3 (shown in red for each compound). Using our rules of thumb, we find that the hydrogens of CH_3O are less shielded (appear farther downfield) than the hydrogens of $CH_3C{=}O$. Table 11.4 gives approximate values for each chemical shift. Experimental values are as follows:

See problem 11.42

PROBLEM 11.12

Following are two constitutional isomers with the molecular formula $C_4H_8O_2$:



(1) (2)

(a) Predict the number of signals in the ^{1}H-NMR spectrum of each isomer.

(b) Predict the ratio of areas of the signals in each spectrum.

(c) Show how to distinguish between these isomers on the basis of chemical shift.

11.11 What Is Signal Splitting?

We have now seen three kinds of information that can be derived from an examination of a ^{1}H-NMR spectrum:

1. From the number of signals, we can determine the number of sets of equivalent hydrogens.
2. By integrating over signal areas, we can determine the relative numbers of hydrogens giving rise to each signal.
3. From the chemical shift of each signal, we can derive information about the types of hydrogens in each set.

We can derive a fourth kind of information from the splitting pattern of each signal. Consider, for example, the ^{1}H-NMR spectrum of 1,1,2-trichloroethane (Figure 11.19), a solvent for waxes and natural resins. This molecule contains two 2° hydrogens and one 3° hydrogen, and, according to what we have learned so far, we predict two signals with relative areas 2 : 1, corresponding to the two hydrogens of the $-CH_2-$ group and the one hydrogen of the $-CHCl_2$ group. You see from the spectrum, however, that there are in fact five **peaks**. How can this be, when we predict only two signals? The answer is that

Peaks (NMR) The units into which an NMR signal is split—two peaks in a doublet, three peaks in a triplet, and so on

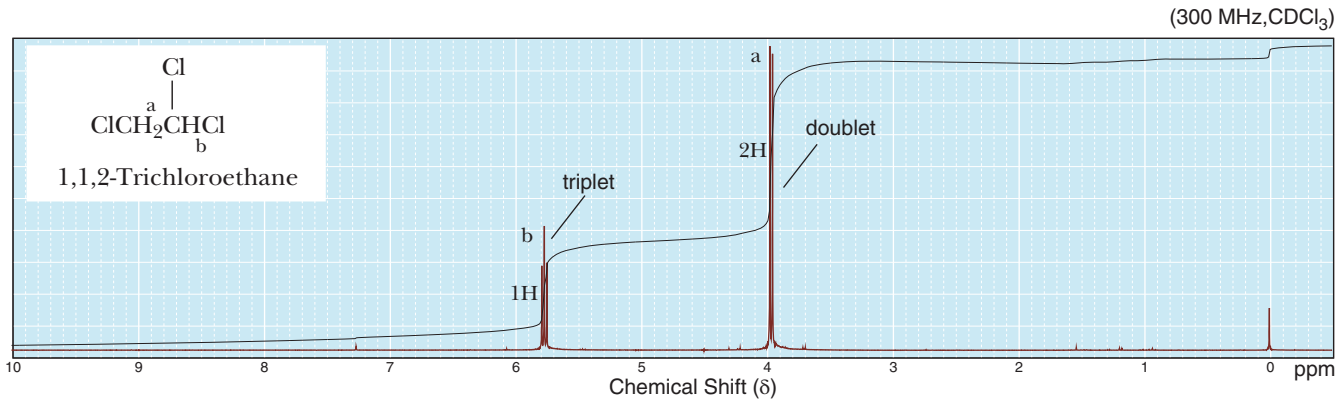


FIGURE 11.19 ^{1}H-NMR spectrum of 1,1,2-trichloroethane.

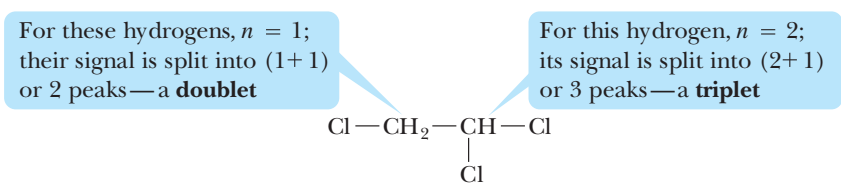
a hydrogen's resonance frequency can be affected by the tiny magnetic fields of other hydrogens close by. Those fields cause the signal to be **split** into numerous peaks.

Hydrogens split each other if they are separated by no more than three bonds—for example, H—C—C—H or H—C═C—H. (There are three bonds in each case.) If there are more than three bonds, as in H—C—C—C—H, then there is normally no splitting. A signal with just one peak is called a **singlet**. A signal that is split into two peaks is called a **doublet**. Signals that are split into three and four peaks are called **triplets** and **quartets**, respectively.

The grouping of two peaks at δ 3.96 in the ^{1}H-NMR spectrum of 1,1,2-trichloroethane is the signal for the hydrogens of the —CH_2— group, and the grouping of three peaks at δ 5.77 is the signal for the single hydrogen of the —$CHCl_2$ group. We say that the CH_2 signal at δ 3.96 is split into a doublet and that the CH signal at δ 5.77 is split into a triplet. In this phenomenon, called **signal splitting**, the ^{1}H-NMR signal from one set of hydrogens is split by the influence of neighboring nonequivalent hydrogens.

The degree of signal splitting can be predicted on the basis of the **(n + 1) rule**, according to which, if a hydrogen has n hydrogens nonequivalent to it, but equivalent among themselves, on the same or adjacent atom(s), then the ^{1}H-NMR signal of the hydrogen is split into (n + 1) peaks.

Let us apply the (n + 1) rule to the analysis of the spectrum of 1,1,2-trichloroethane. The two hydrogens of the —CH_2— group have one nonequivalent neighboring hydrogen (n = 1); their signal is split into a doublet (1 + 1 = 2). The single hydrogen of the —$CHCl_2$ group has a set of two nonequivalent neighboring hydrogens (n = 2); its signal is split into a triplet (2 + 1 = 3).



It is important to remember that the (n + 1) rule of signal splitting applies only to hydrogens with *equivalent* neighboring hydrogens. When more than one set of neighboring hydrogens exists, the (n + 1) rule no longer applies. An example of where the (n + 1) rule no longer applies is illustrated in the ^{1}H-NMR spectrum of 1-chloropropane. The two hydrogens on carbon 2 (a CH_2 group) of 1-chloropropane are flanked on one side by a set of 2H on carbon 1, and on the other side by a set of 3H on carbon 3. Because the sets of hydrogen on carbons 1 and 3 are nonequivalent to each

Singlet A signal that consists of one peak; the hydrogens that give rise to the signal have no neighboring nonequivalent hydrogens.

Doublet A signal that is split into two peaks; the hydrogens that give rise to the signal have one neighboring nonequivalent hydrogen.

Triplets A signal that is split into three peaks; the hydrogens that give rise to the signal have two neighboring nonequivalent hydrogens that are equivalent to each other.

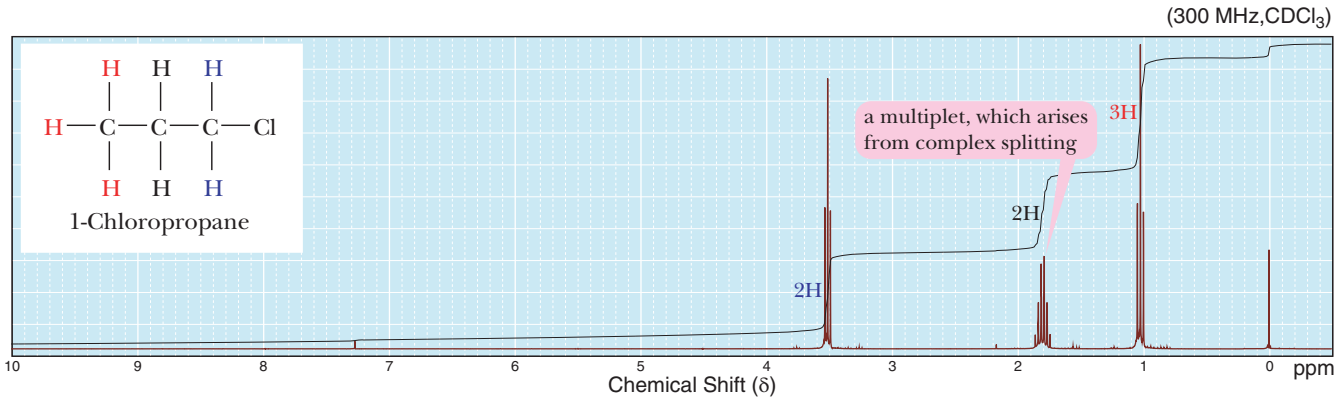
Quartets A signal that is split into four peaks; the hydrogens that give rise to the signal have three neighboring nonequivalent hydrogens that are equivalent to each other.

Signal splitting Splitting of an NMR signal into a set of peaks by the influence of neighboring nuclei.

(n + 1) rule The ^{1}H-NMR signal of a hydrogen or set of equivalent hydrogens with n other hydrogens on neighboring carbons is split into (n + 1) peaks.

Multiplet A signal that is split into multiple peaks, often of an irregular pattern, due to the presence of more than one type of neighboring hydrogens.

other and also nonequivalent to the hydrogens on carbon 2, they cause the signal for the CH_2 group on carbon 2 to be split into a complex pattern, which we will refer to simply as a **multiplet**.



EXAMPLE 11.13

Predict the number of signals and the splitting pattern of each signal in the ^{1}H-NMR spectrum of each compound.

(a) $CH_3CCH_2CH_3$ (O) **(b)** $CH_3CH_2CCH_2CH_3$ (O) **(c)** $CH_3CCH(CH_3)_2$ (O)

STRATEGY

Determine the number of signals by determining the number of equivalent hydrogens (Section 11.8). For each set of equivalent hydrogens, determine the number of equivalent neighbors (n) and apply the (n + 1) rule to determine the splitting pattern.

SOLUTION

The sets of equivalent hydrogens in each molecule are color coded. In molecule (a), the signal for the red methyl group is unsplit (a singlet) because the group is too far (>3 bonds) from any other hydrogens. The blue —CH_2— group has three neighboring hydrogens ($n = 3$) and thus shows a signal split into a quartet ($3 + 1 = 4$). The green methyl group has two neighboring hydrogens ($n = 2$), and its signal is split into a triplet. The integration ratios for these signals would be 3 : 2 : 3. Parts (b) and (c) can be analyzed in the same way. Thus, molecule (b) shows a triplet and a quartet in the ratio 3 : 2. Molecule (c) shows a singlet, a septet ($6 + 1 = 7$), and a doublet in the ratio 3 : 1 : 6.

(a) singlet, quartet, triplet: $CH_3—C(=O)—CH_2—CH_3$ **(b)** triplet, quartet: $CH_3—CH_2—C(=O)—CH_2—CH_3$ **(c)** singlet, septet, doublet: $CH_3—C(=O)—CH(CH_3)_2$

See problem 11.32

PROBLEM 11.13

Following are pairs of constitutional isomers. Predict the number of signals and the splitting pattern of each signal in the ^{1}H-NMR spectrum of each isomer.

(a) $CH_3OCH_2CCH_3$ (O) and $CH_3CH_2COCH_3$ (O) **(b)** CH_3CCH_3 (Cl) and $ClCH_2CH_2CH_2Cl$

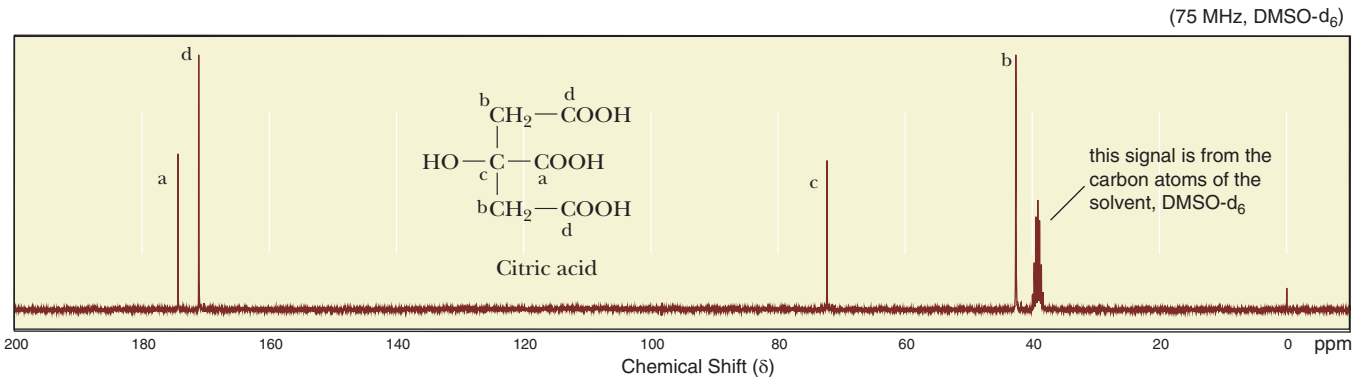


FIGURE 11.20 Hydrogen-decoupled ^{13}C-NMR spectrum of citric acid.

11.12 What Is ^{13}C-NMR Spectroscopy, and How Does It Differ from ^{1}H-NMR Spectroscopy?

Nuclei of carbon-12, the most abundant (98.89%) natural isotope of carbon, do not have nuclear spin and are not detected by NMR spectroscopy. Nuclei of carbon-13 (natural abundance 1.11%), however, do have nuclear spin and are detected by NMR spectroscopy in the same manner as hydrogens are detected. Thus, NMR can be used to obtain information about 1.11% of all the carbon atoms in a sample. Just as in ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy yields a signal for each set of equivalent carbons in a molecule.

Because both ^{13}C and ^{1}H have spinning nuclei and generate magnetic fields, ^{13}C couples with each ^{1}H bonded to it and gives a signal split according to the $(n + 1)$ rule. In the most common mode for recording a ^{13}C spectrum, this coupling is eliminated by instrumental techniques, so as to simplify the spectrum. In these **hydrogen-decoupled spectra**, all ^{13}C signals appear as singlets. The hydrogen-decoupled ^{13}C-NMR spectrum of citric acid (Figure 11.20), a compound used to increase the solubility of many pharmaceutical drugs in water, consists of four singlets. Again, notice that, as in ^{1}H-NMR, equivalent carbons generate only one signal.

Chemical Connections 11C

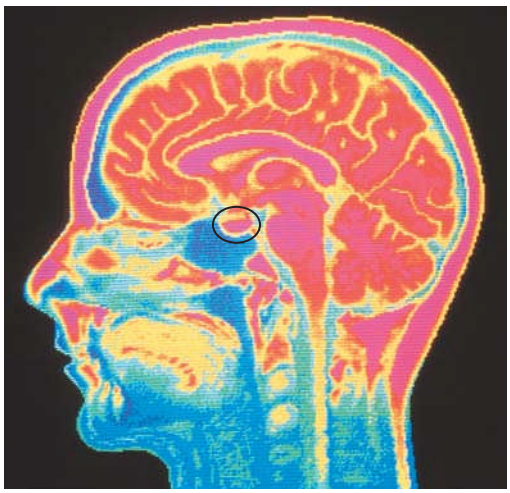
MAGNETIC RESONANCE IMAGING (MRI)

Nuclear magnetic resonance was discovered and explained by physicists in the 1950s, and, by the 1960s, it had become an invaluable analytical tool for chemists. By the early 1970s, it was realized that the imaging of parts of the body via NMR could be a valuable addition to diagnostic medicine. Because the term *nuclear magnetic resonance* sounds to many people as if the technique might involve radioactive material, health care personnel call the technique *magnetic resonance imaging* (MRI).

The body contains several nuclei that, in principle, could be used for MRI. Of these, hydrogens, most of which come from water, triglycerides (fats), and membrane phospholipids, give the most useful signals. Phosphorus MRI is also used in diagnostic medicine.

Recall that, in NMR spectroscopy, energy in the form of radio-frequency radiation is absorbed by nuclei in the sample. The relaxation time is the characteristic time at which excited nuclei give up this energy and relax to their ground state.

In 1971, Raymond Damadian discovered that the relaxation of water in certain cancerous tumors takes much longer than the relaxation of water in normal cells. Thus, it was reasoned that if a relaxation image of the body could be obtained, it might be possible to identify tumors at an early stage. Subsequent work demonstrated that many tumors can be identified in this way.



Mehau Kulyk/Photo Researchers, Inc

Computer-enhanced MRI scan of a normal human brain with pituitary gland circled.

Another important application of MRI is in the examination of the brain and spinal cord. White and gray matter, the two different layers of the brain, are easily distinguished by MRI, which is useful in the study of such diseases as multiple sclerosis. Magnetic resonance imaging and X-ray imaging are in many cases complementary: The hard, outer layer of bone is essentially invisible to MRI, but shows up extremely well in X-ray images, whereas soft tissue is nearly transparent to X rays, but shows up in MRI.

The key to any medical imaging technique is knowing which part of the body gives rise to which signal. In MRI, the patient is placed in a magnetic field gradient that can be varied from place to place. Nuclei in the weaker magnetic field gradient absorb radiation at a lower frequency. Nuclei elsewhere, in the stronger magnetic field, absorb radiation at a higher frequency. Because a magnetic field gradient along a single axis images a plane, MRI techniques can create views of any part of the body in slicelike sections. In 2003, Paul Lauterbur and Sir Peter Mansfield were awarded the Nobel Prize in Physiology or Medicine for their discoveries that led to the development of these imaging techniques.

Question

In ^{1}H-NMR spectroscopy, the chemical sample is set spinning on its long axis to ensure that all parts of the sample experience a homogeneous applied field. Homogeneity is also required in MRI. Keeping in mind that the "sample" in MRI is a human being, how do you suppose this is achieved?

Table 11.5 shows approximate chemical shifts in ^{13}C-NMR spectroscopy. As with ^{1}H-NMR, we can use the following rules of thumb to remember the chemical shifts of various types of carbons:

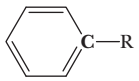
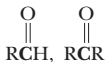
follow these rules of thumb for most ^{13}C-NMR spectra problems

Chemical Shift (δ)	Type of Carbon
0–50	sp^3 carbon (3° > 2° > 1°).
50–80	sp^3 carbon bonded to an electronegative element such as N, O, or X. The more electronegative the element, the larger is the chemical shift.
100–160	sp^2 carbon of an alkene or an aromatic compound.
160–180	carbonyl carbon of a carboxylic acid or carboxylic acid derivative (Chapters 13 and 14).
180–210	carbonyl carbon of a ketone or an aldehyde (Chapter 12).

Notice how much broader the range of chemical shifts is for ^{13}C-NMR spectroscopy (0–210 ppm) than for ^{1}H-NMR spectroscopy (0–12 ppm). Because of this expanded scale, it is very unusual to find any two nonequivalent carbons in the same molecule with identical chemical shifts. Most commonly, each different type of carbon within a molecule has a distinct signal that is clearly resolved (i.e., separated) from all other signals. Notice further that the chemical shift of carbonyl carbons is quite distinct from the chemical shifts of sp^3 hybridized carbons and other types of sp^2 hybridized carbons. The presence or absence of a carbonyl carbon is quite easy to recognize in a ^{13}C-NMR spectrum.

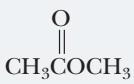
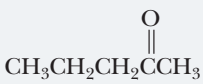
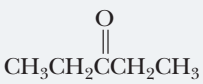
A great advantage of ^{13}C-NMR spectroscopy is that it is generally possible to count the number of different types of carbon atoms in a molecule. There is one caution here, however: Because of the particular manner in which spin-flipped ^{13}C nuclei return to their lower energy states, integrating signal areas is often unreliable, and it is generally not possible to determine the number of carbons of each type on the basis of the signal areas.

TABLE 11.5 ^{13}C-NMR Chemical Shifts

Type of Carbon	Chemical Shift (δ)	Type of Carbon	Chemical Shift (δ)
RCH_3	0–40		110–160
RCH_2R	15–55		
R_3CH	20–60		
RCH_2I	0–40		160–180
RCH_2Br	25–65		
RCH_2Cl	35–80		165–180
R_3COH	40–80		
R_3COR	40–80		175–185
$RC{\equiv}CR$	65–85		
$R_2C{=}CR_2$	100–150		180–210

EXAMPLE 11.14

Predict the number of signals in a proton-decoupled ^{13}C-NMR spectrum of each compound:

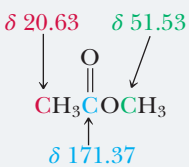
(a)  (b)  (c) 

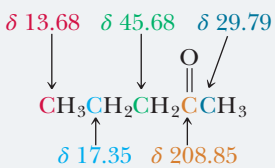
STRATEGY

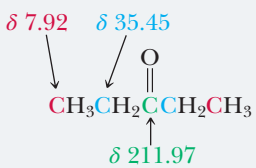
Because we cannot replace each carbon atom with a halogen (as we did to determine equivalency in ^{1}H-NMR), inasmuch as a halogen only has a valence of 1, we will need to use symmetry to determine equivalency.

SOLUTION

Here is the number of signals in each spectrum, along with the chemical shift of each, color coded to the carbon responsible for that signal. The chemical shifts of the carbonyl carbons are quite distinctive (Table 11.5) and occur at δ 171.37, 208.85, and 211.97 in these examples.

(a) 

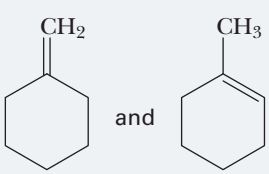
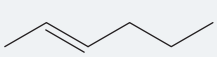
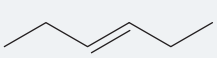
(b) 

(c) 

See problem 11.33

PROBLEM 11.14

Explain how to distinguish between the members of each pair of constitutional isomers, on the basis of the number of signals in the ^{13}C-NMR spectrum of each isomer:

(a)  and (b)  and 

11.13 How Do We Solve an NMR Problem?

One of the first steps in determining the molecular structure of a compound is to establish the compound's molecular formula. In the past, this was most commonly done by elemental analysis, combustion to determine the percent composition, and so forth. More commonly today, we determine molecular weight and molecular formula by a technique known as *mass spectrometry* (an explanation of the technique is beyond the scope of this book). In the examples that follow, we assume that the molecular formula of any unknown compound has already been determined, and we proceed from there, using spectral analysis to determine a structural formula.

The following steps may prove helpful as a systematic approach to solving ^{1}H-NMR spectral problems:

Step 1: **Molecular formula and IHD.** Examine the molecular formula, calculate the IHD (Section 11.4G), and deduce what information you can about the presence or absence of rings or pi bonds.

Step 2: **Number of signals.** Count the number of signals to determine the minimum number of sets of equivalent hydrogens in the compound.

Step 3: **Integration.** Use signal integration and the molecular formula to determine the number of hydrogens in each set.

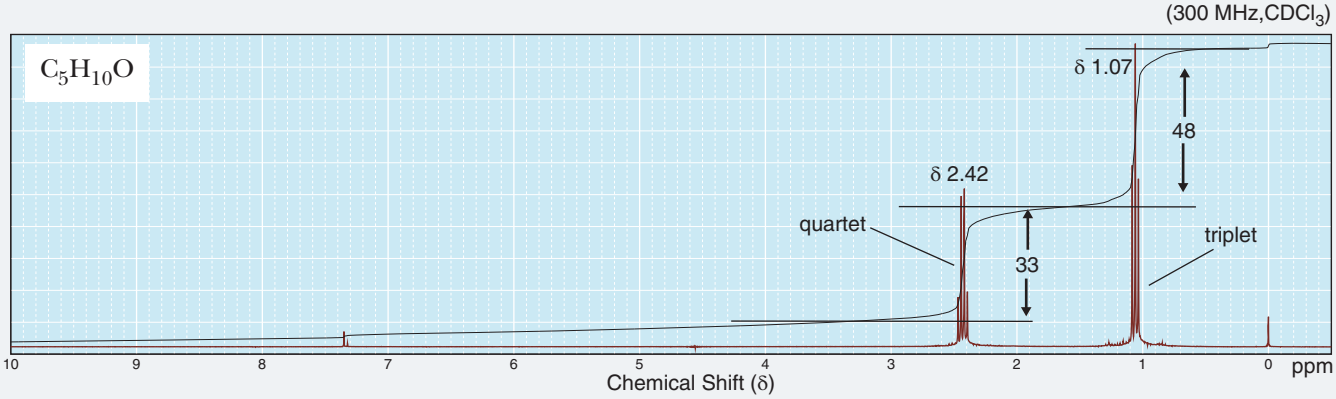
Step 4: **Pattern of chemical shifts.** Examine the ^{1}H-NMR spectrum for signals characteristic of the most common types of equivalent hydrogens. (See the general rules of thumb for ^{1}H-NMR chemical shifts in Section 11.10.) Keep in mind that the ranges are broad and that hydrogens of each type may be shifted either farther upfield or farther downfield, depending on details of the molecular structure in question.

Step 5: **Splitting patterns.** Examine splitting patterns for information about the number of nonequivalent hydrogen neighbors.

Step 6: **Structural formula.** Write a structural formula consistent with the information learned in Steps 1–5.

EXAMPLE 11.15

Following is a ^{1}H-NMR spectrum for a compound that is a colorless liquid with the molecular formula $C_5H_{10}O$. Propose a structural formula for the compound.



STRATEGY

^{1}H-NMR spectra can be approached by (1) calculating the IHD and deducing what information you can about the presence or absence of rings or pi bonds, (2) counting the number of signals to determine the minimum number of sets of equivalent hydrogens in the compound, (3) using signal integration and the molecular formula to determine the number of hydrogens in

each set, (4) examining the NMR spectrum for signals characteristic of the most common types of equivalent hydrogens, (5) examining splitting patterns for information about the number of nonequivalent hydrogen neighbors, and (6) writing a structural formula consistent with the information learned in Steps 1–5.

SOLUTION

STEP 1: *Molecular formula and IHD.*
The reference compound is $C_5H_{12}O$; therefore, the IHD is 1. The molecule thus contains either one ring or one pi bond.

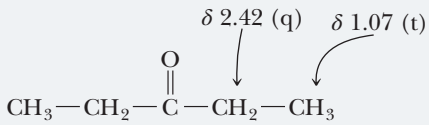
STEP 2: *Number of signals.*
There are two signals (a triplet and a quartet) and therefore two sets of equivalent hydrogens.

STEP 3: *Integration.*
By signal integration, we calculate that the number of hydrogens giving rise to each signal is in the ratio 3 : 2. Because there are 10 hydrogens, we conclude that the signal assignments are δ 1.07 (6H) and δ 2.42 (4H).

STEP 4: *Pattern of chemical shifts.*
The signal at δ 1.07 is in the alkyl region and, based on its chemical shift, most probably represents a methyl group. No signal occurs at δ 4.6 to 5.7; thus, there are no vinylic hydrogens. (If a carbon–carbon double bond is in the molecule, no hydrogens are on it; that is, it is tetrasubstituted.)

STEP 5: *Splitting pattern.*
The methyl signal at δ 1.07 is split into a triplet (t); hence, it must have two neighboring hydrogens, indicating —CH_2CH_3. The signal at δ 2.42 is split into a quartet (q); thus, it must have three neighboring hydrogens, which is also consistent with —CH_2CH_3. Consequently, an ethyl group accounts for these two signals. No other signals occur in the spectrum; therefore, there are no other types of hydrogens in the molecule.

STEP 6: *Structural formula.*
Put the information learned in the previous steps together to arrive at the following structural formula. Note that the chemical shift of the methylene group (—CH2—) at δ 2.42 is consistent with an alkyl group adjacent to a carbonyl group.

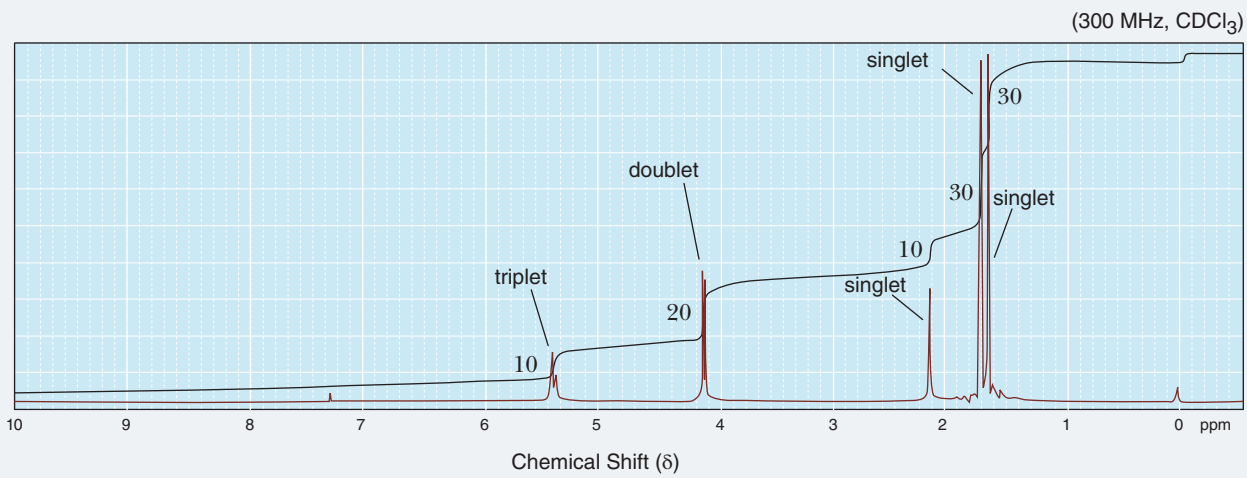


3-Pentanone

See problems 11.35–11.37, 11.39–11.62

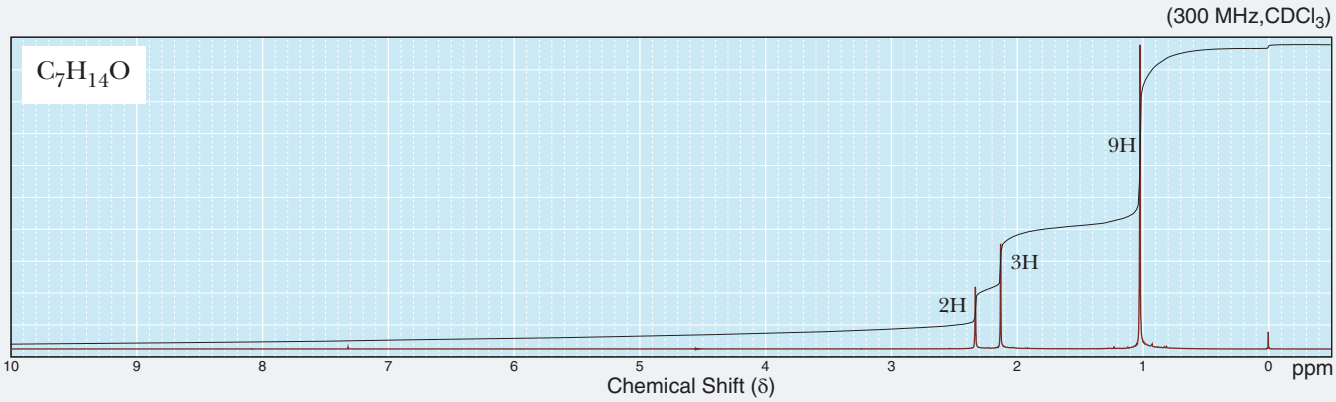
PROBLEM 11.15

Following is a ^{1}H-NMR spectrum for prenol, a compound that possesses a fruity odor and that is commonly used in perfumes. Prenol has the molecular formula $C_5H_{10}O$. Propose a structural formula for prenol.



EXAMPLE 11.16

Following is a ^{1}H-NMR spectrum for a compound that is a colorless liquid with the molecular formula $C_7H_{14}O$. Propose a structural formula for the compound.



STRATEGY

^{1}H-NMR spectra can be approached by (1) calculating the IHD and deducing what information you can about the presence or absence of rings or pi bonds, (2) counting the number of signals to determine the minimum number of sets of equivalent hydrogens in the compound, (3) using signal integration and the molecular formula to determine the number of hydrogens in each set, (4) examining the NMR spectrum for signals characteristic of the most common types of equivalent hydrogens, (5) examining splitting patterns for information about the number of nonequivalent hydrogen neighbors, and (6) writing a structural formula consistent with the information learned in Steps 1–5.

SOLUTION

STEP 1: *Molecular formula and IHD.*
The IHD is 1; thus, the compound contains one ring or one pi bond.

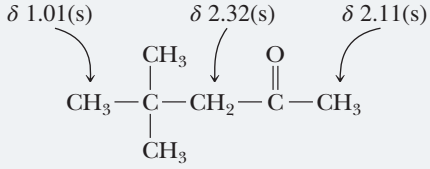
STEP 2: *Number of signals.*
There are three signals and therefore three sets of equivalent hydrogens.

STEP 3: *Integration.*
By signal integration, we calculate that the number of hydrogens giving rise to each signal is in the ratio 2 : 3 : 9, reading from left to right.

STEP 4: *Pattern of chemical shifts.*
The singlet at δ 1.01 is characteristic of a methyl group adjacent to an sp^3 hybridized carbon. The singlets at δ 2.11 and 2.32 are characteristic of alkyl groups adjacent to a carbonyl group.

STEP 5: *Splitting pattern.*
All signals are singlets (s), which means that none of the hydrogens are within three bonds of each other.

STEP 6: *Structural formula.*
The compound is 4,4-dimethyl-2-pentanone:

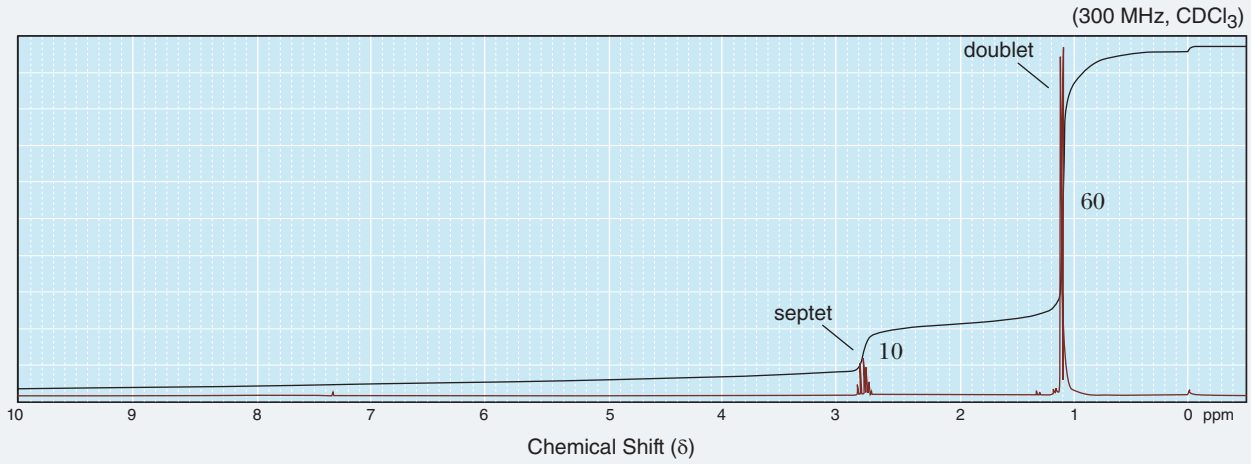


4,4-Dimethyl-2-pentanone

See problems 11.35–11.37, 11.39–11.62

PROBLEM 11.16

Following is a ^{1}H-NMR spectrum for a compound that is a colorless liquid with the molecular formula $C_7H_{14}O$. Propose a structural formula for the compound.



The following steps may prove helpful as a systematic approach to solving ^{13}C-NMR spectral problems:

Step 1: **Molecular formula and IHD.** Examine the molecular formula, calculate the IHD (Section 11.4G), and deduce what information you can about the presence or absence of rings or pi bonds.

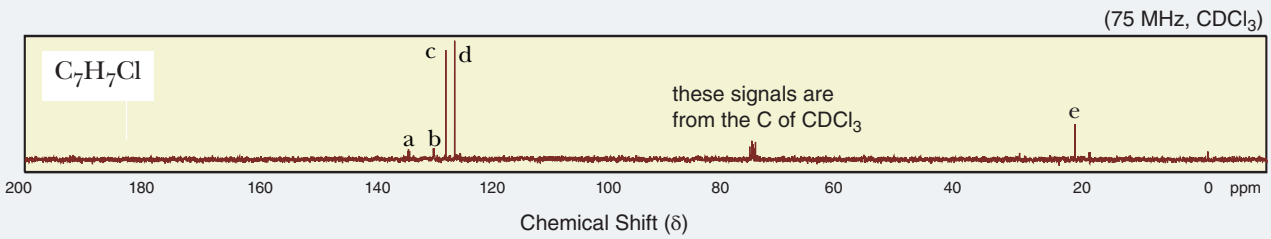
Step 2: **Number of signals.** Count the number of signals to determine the minimum number of sets of equivalent carbons in the compound.

Step 3: **Pattern of chemical shifts.** Examine the NMR spectrum for signals characteristic of the most common types of equivalent carbons (see the general rules of thumb for ^{13}C-NMR chemical shifts in Section 11.12). Keep in mind that these ranges are broad and that carbons of each type may be shifted either farther upfield or farther downfield, depending on details of the molecular structure in question.

Step 4: **Structural formula.** Write a structural formula consistent with the information learned in Steps 1–3. *Note*: Because ^{13}C-NMR does not provide information about neighboring hydrogens, it may be more difficult to elucidate the structure of a compound based solely on ^{13}C-NMR data.

EXAMPLE 11.17

Following is a ^{13}C-NMR spectrum for a compound that is a colorless liquid with the molecular formula C_7H_7Cl. Propose a structural formula for the compound.



STRATEGY

^{13}C-NMR spectra can be approached by (1) calculating the IHD and deducing what information you can about the presence or absence of rings or pi bonds, (2) counting the number of signals to determine the minimum number of sets of equivalent carbons in the compound, (3) examining the NMR spectrum for signals characteristic of the most common types of equivalent carbons, and (4) writing a structural formula consistent with the information learned in Steps 1–3.

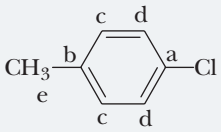
SOLUTION

STEP 1: *Molecular formula and IHD.*
The IHD is 4; thus, the compound can contain a myriad combination of rings or pi bonds.

STEP 2: *Number of signals.*
There are five signals and therefore five sets of equivalent carbons. Because there are seven carbons total, there must be symmetry in the molecule.

STEP 3: *Pattern of chemical shifts.*
The signal (e) at δ 23 is characteristic of an sp^3 hybridized carbon. The four signals **(a–d)** between δ 120 and 140 are characteristic of sp^2 hybridized carbons. Because it would be unlikely for a molecule with only seven carbon atoms to have 4 pi bonds (due to IHD = 4), it is likely that these signals represent the carbons of a benzene ring.

STEP 4: *Structural formula.*
Because there must be symmetry in the molecule, the most likely structure of the compound is:

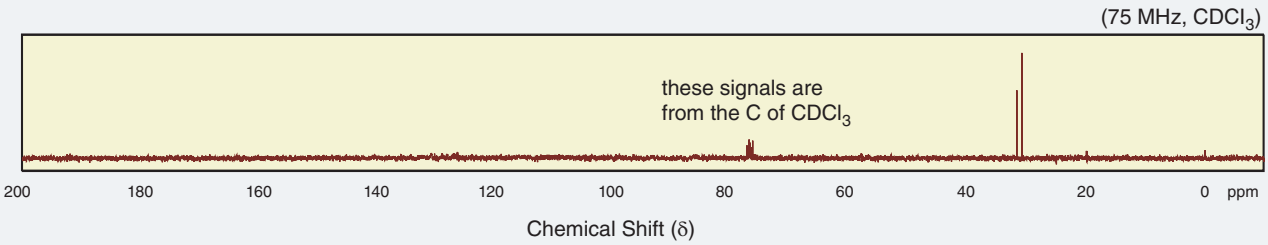


4-Chlorotoluene

See problems 11.34, 11.38, 11.39, 11.43, 11.44, 11.50–11.54

PROBLEM 11.17

Following is a ^{13}C-NMR spectrum for a compound that is a colorless liquid with the molecular formula $C_4H_8Br_2$. Propose a structural formula for the compound.



SUMMARY OF KEY QUESTIONS

11.1 What Is Electromagnetic Radiation?

- **Electromagnetic radiation** is a wave traveling at the speed of light that can be described in terms of its **wavelength** (λ) and its **frequency** (ν).
- Frequency is reported in **hertz (Hz)**.
- An alternative way to describe electromagnetic radiation is in terms of its energy where $E = h\nu$.

11.2 What Is Molecular Spectroscopy?

- **Molecular spectroscopy** is the experimental process of measuring which frequencies of radiation are absorbed or emitted by a substance and correlating these patterns with details of molecular structure.

11.3 What Is Infrared Spectroscopy?

- **Infrared spectroscopy** is molecular spectroscopy applied to frequencies of infrared radiation.
- Interactions of molecules with **infrared radiation** excite covalent bonds to higher vibrational energy levels.
- The **vibrational infrared** spectrum extends from 4000 to 400 cm^{-1}. Radiation in this region is referred to by its wavenumber ($\bar{\nu}$) in reciprocal centimeters (cm^{-1}).

- To be **infrared active**, a bond must be polar; the more polar it is, the stronger is its absorption of IR radiation.
- The simplest vibrations that give rise to the absorption of infrared radiation are **stretching** and **bending** vibrations.
- Stretching may be symmetrical or asymmetrical.
- A **correlation table** is a list of the absorption patterns of functional groups. The intensity of a peak is referred to as **strong** (**s**), **medium** (**m**), or **weak** (**w**). Stretching vibrations for most functional groups appear in the region from 3400 to 1000 cm^{-1}.
- The region from 1000 to 400 cm^{-1} is referred to as the **fingerprint region**, so called because absorption bands in this region are unique to each compound.

11.4 How Do We Interpret Infrared Spectra?

- The **index of hydrogen deficiency (IHD)** is the sum of the number of rings and pi bonds in a molecule. It can be determined by comparing the number of hydrogens in the molecular formula of a compound of unknown structure with the number of hydrogens in a reference compound with the same number of carbon atoms and with no rings or pi bonds.
- Using the IHD along with knowledge of characteristic IR absorptions for various functional groups, one can determine the possible structures for an unknown whose molecular formula is known.

11.5 What Is Nuclear Magnetic Resonance?

- An atomic nucleus that has an odd mass or an odd atomic number also has a **spin** and behaves as if it were a tiny bar magnet.
- When a collection of ^1H and ^{13}C atoms is placed between the poles of a powerful magnet, interactions between their nuclear spins and the applied magnetic field are quantized, and only two orientations are allowed.
- When placed between the poles of a powerful magnet, the nuclear spins of these elements become aligned either with the applied field or against it.
- Nuclear spins aligned with the applied field are in the lower energy state; those aligned against the applied field are in the higher energy state.
- **Resonance** is the absorption of electromagnetic radiation by a nucleus and the resulting "flip" of its nuclear spin from a lower energy spin state to a higher energy spin state.

11.6 What Is Shielding?

- The experimental conditions required to cause nuclei to resonate are affected by the local chemical and magnetic environment.
- Electrons around a hydrogen also have spin and create a local magnetic field that **shields** the hydrogen from the applied field.

11.7 What Is an NMR Spectrum?

- An **NMR spectrometer** records resonance as a signal, and the collection of all resonance signals for a sample is its **NMR spectrum**.

11.8 How Many Resonance Signals Will a Compound Yield in Its ^1H-NMR Spectrum?

- **Equivalent hydrogens** within a molecule have identical chemical shifts.

11.9 What Is Signal Integration?

- The area of a ^1H-NMR signal is proportional to the number of equivalent hydrogens giving rise to that **signal**. Determination of these areas is termed **integration**.

11.10 What Is Chemical Shift?

- In a ^1H-NMR spectrum, a resonance signal is reported by how far it is shifted from the resonance signal of the 12 equivalent hydrogens in **tetramethylsilane (TMS)**.
- A resonance signal in a ^{13}C-NMR spectrum is reported by how far it is shifted from the resonance signal of the four equivalent carbons in TMS.
- A **chemical shift** (δ) is the frequency shift from TMS, divided by the operating frequency of the spectrometer.

11.11 What Is Signal Splitting?

- In **signal splitting**, the ^1H-NMR signal from one hydrogen or set of equivalent hydrogens is split by the influence of nonequivalent hydrogens on the same or adjacent carbon atoms.
- According to the **(n + 1) rule**, if a hydrogen has n hydrogens that are nonequivalent to it, but are equivalent among themselves, on the same or adjacent carbon atom(s), its ^1H-NMR signal is split into (n + 1) peaks.
- **Complex splitting** occurs when a hydrogen is flanked by two or more sets of hydrogens and those sets are nonequivalent.
- Splitting patterns are commonly referred to as **singlets**, **doublets**, **triplets**, **quartets**, **quintets**, and **multiplets**.

11.12 What Is ^{13}C-NMR Spectroscopy, and How Does It Differ from ^1H-NMR Spectroscopy?

- A ^{13}C-NMR spectrum normally spans the range δ 0–210 (versus δ 0–13 for ^1H-NMR).
- ^{13}C-NMR spectra are commonly recorded in a **hydrogen-decoupled** instrumental mode. In this mode, all ^{13}C signals appear as singlets.
- Integration is not normally performed in ^{13}C-NMR.

11.13 How Do We Solve an NMR Problem?

- ^1H-NMR spectra can be approached by (1) calculating the IHD and deducing what information you can about the presence or absence of rings or pi bonds, (2) counting the number of signals to determine the minimum number of sets of equivalent hydrogens in the compound, (3) using signal integration and the molecular formula to determine the number of hydrogens in each set, (4) examining the NMR spectrum for signals characteristic of the most common types of equivalent hydrogens, (5) examining splitting

patterns for information about the number of nonequivalent hydrogen neighbors, and (6) writing a structural formula consistent with the information learned in Steps 1–5.

- ^{13}C-NMR spectra can be approached by (1) calculating the IHD and deducing what information you can about the presence or absence of rings or pi bonds, (2) counting the number of signals to determine the minimum number of sets of equivalent carbons in the compound, (3) examining the NMR spectrum for signals characteristic of the most common types of equivalent carbons, and (4) writing a structural formula consistent with the information learned in Steps 1–3.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. A weak absorption band in an infrared spectrum can be attributed to, among other things, absorption of infrared light by a low polarity bond. (11.3)

2. Integration reveals the number of neighboring hydrogens in a ^{1}H-NMR spectrum. (11.11)

3. Wavelength and frequency are directly proportional. That is, as wavelength increases, frequency increases. (11.1)

4. An alkene (vinylic) hydrogen can be distinguished from a benzene ring hydrogen via ^{1}H-NMR spectroscopy. (11.10)

5. IR spectroscopy can be used to distinguish between a terminal alkyne and an internal alkyne. (11.4)

6. The NMR signal of a shielded nucleus appears more upfield than the signal for a deshielded nucleus. (11.7)

7. A transition between two energy states, E_1 and E_2, can be made to occur using light equal to or greater than the energy difference between E_1 and E_2. (11.2)

8. The chemical shift of a nucleus depends on its resonance frequency. (11.7)

9. A compound with the molecular formula $C_5H_{10}O$ could contain a C—C triple bond, two C═O bonds, or two rings. (11.4)

10. A ketone can be distinguished from an aldehyde via ^{13}C-NMR spectroscopy. (11.12)

11. A compound with the molecular formula $C_7H_{12}O$ has an IHD of 2. (11.4)

12. A ^{1}H-NMR spectrum with an integration ratio of 3:1:2 could represent a compound with the molecular formula C_5H_9O. (11.9)

13. Electromagnetic radiation can be described as a wave, as a particle, and in terms of energy. (11.1)

14. A set of hydrogens are equivalent if replacing each of them with a halogen results in compounds of the same name. (11.8)

15. The collection of absorption peaks in the 1000–400 cm^{-1} region of an IR spectrum is unique to a particular compound (i.e., no two compounds will yield the same spectrum in this region). (11.3)

16. The area under each peak in a ^{1}H-NMR spectrum can be determined using a technique known as integration. (11.9)

17. All atomic nuclei have a spin, which allows them to be analyzed by NMR spectroscopy. (11.5)

18. C—H stretching vibrations occur at higher wavenumbers than C—C stretching vibrations. (11.4)

19. The resonance frequency of a nucleus depends on its amount of shielding. (11.6)

20. It is not possible to use IR spectroscopy to distinguish between a ketone and a carboxylic acid. (11.4)

21. A carboxylic acid can be distinguished from an aldehyde via ^{1}H-NMR spectroscopy. (11.10)

22. A wavenumber, $\bar{\nu}$, is directly proportional to frequency. (11.3)

23. Resonance is the excitation of a magnetic nucleus in one spin state to a higher spin state. (11.5)

24. IR spectroscopy cannot be used to distinguish between an alcohol and an ether. (11.4)

25. A compound with an IHD of 1 can contain either one ring, one double bond, or one triple bond. (11.4)

26. Infrared spectroscopy measures transitions between electronic energy levels. (11.2)

27. A set of hydrogens represented by a doublet indicates that there are two neighboring equivalent hydrogens. (11.11)

28. The IHD can reveal the possible number of rings, double bonds, or triple bonds in a compound based solely on its molecular formula. (11.4)

29. TMS, tetramethylsilane, is a type of solvent used in NMR spectroscopy. (11.7)

30. Light of wavelength 400 nm is higher in energy than light of wavelength 600 nm. (11.1)

31. The methyl carbon of 1-chlorobutane will yield a ^{1}H-NMR signal that appears as a triplet. (11.11)

32. A compound with the molecular formula $C_6H_{14}FN$ has an IHD of 1. (11.4)

33. IR spectroscopy can be used to distinguish between 1°, 2°, and 3° amines. (11.4)

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) F (3) F (4) T (5) T (6) T (7) F (8) T (9) F (10) F (11) T (12) F (13) T (14) T (15) T (16) T (17) F (18) T (19) T (20) F (21) T (22) T (23) T (24) F (25) F (26) F (27) F (28) T (29) F (30) T (31) T (32) F (33) T

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 11.1 Electromagnetic Radiation

11.18 Which puts out light of higher energy, a green laser pointer or a red laser pointer? **(See Example 11.1)**

11.19 Calculate the energy, in kilocalories per mole of radiation, of a wave with wavelength 2 m. What type of radiant energy is this? **(See Example 11.1)**

11.20 A molecule possesses molecular orbitals that differ in energy by 82 kcal/mol. What wavelength of light would be required to cause a transition between these two energy levels? What region of the electromagnetic spectrum does this energy correspond to? **(See Example 11.1)**

SECTION 11.4 Interpreting Infrared Spectra

***11.21** Calculate the IHD of each compound: **(See Examples 11.5, 11.6)**

(a) Aspirin, $C_9H_8O_4$

(b) Ascorbic acid (vitamin C), $C_6H_8O_6$

(c) Pyridine, C_5H_5N

(d) Urea, CH_4N_2O

(e) Cholesterol, $C_{27}H_{46}O$

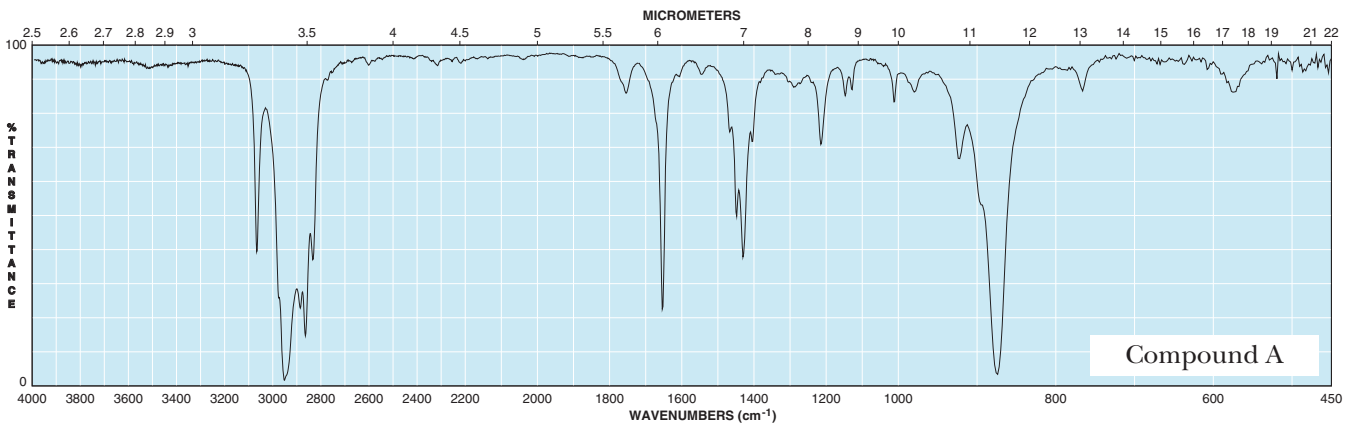
(f) Trichloroacetic acid, $C_2HCl_3O_2$

11.22 Compound A, with the molecular formula C_6H_{10}, reacts with H_2/Ni to give compound B, with the molecular formula C_6H_{12}. The IR spectrum of compound A is provided. From this information about compound A tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound A.

(c) What structural feature(s) would account for compound A's IHD.

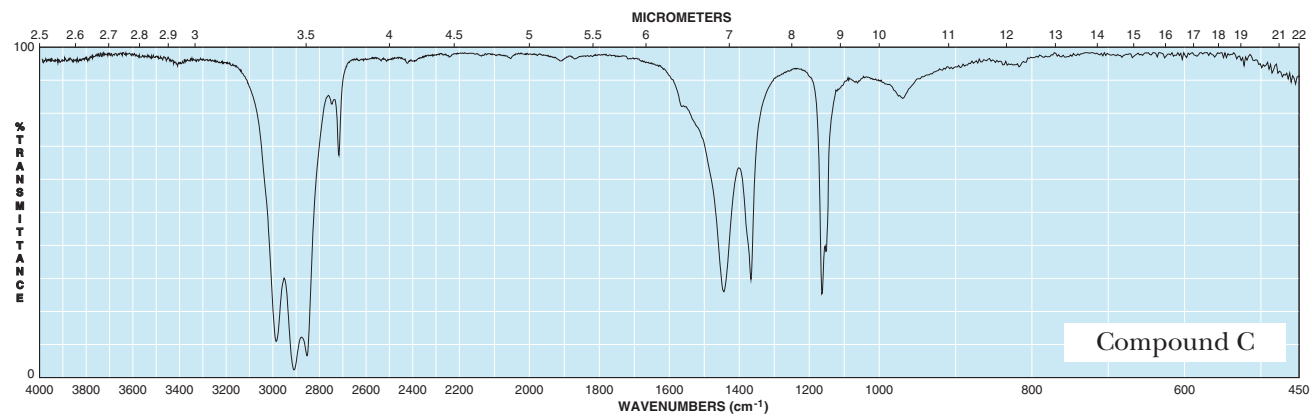


11.23 Compound C, with the molecular formula C_6H_{12}, reacts with H_2/Ni to give compound D, with the molecular formula C_6H_{14}. The IR spectrum of compound C is provided. From this information about compound C, tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound C.

(c) What structural feature(s) would account for compound C's IHD.



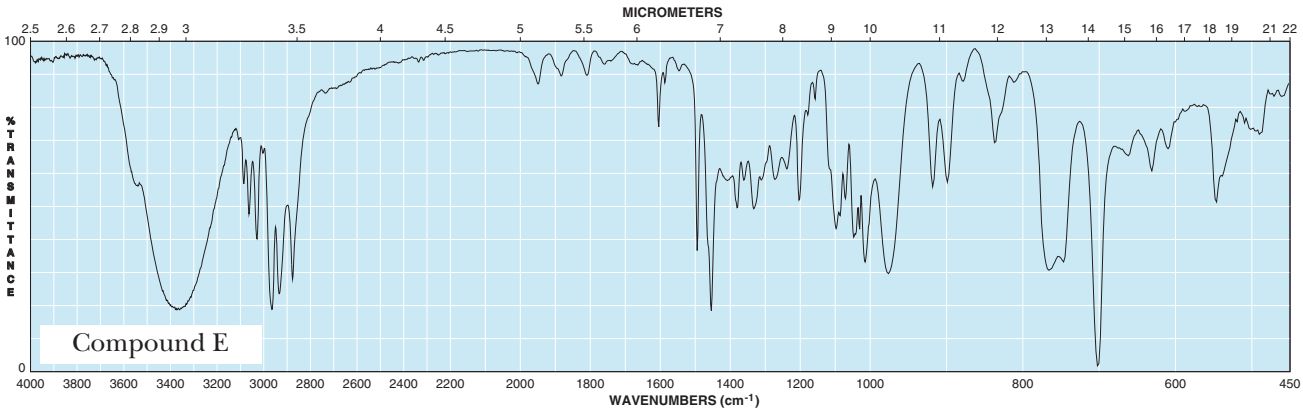
11.24 Examine the following IR spectrum and the molecular formula of compound E, $C_9H_{12}O$: Tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound E.

(c) What one structural feature would account for this IHD.

(d) What oxygen-containing functional group compound E contains.

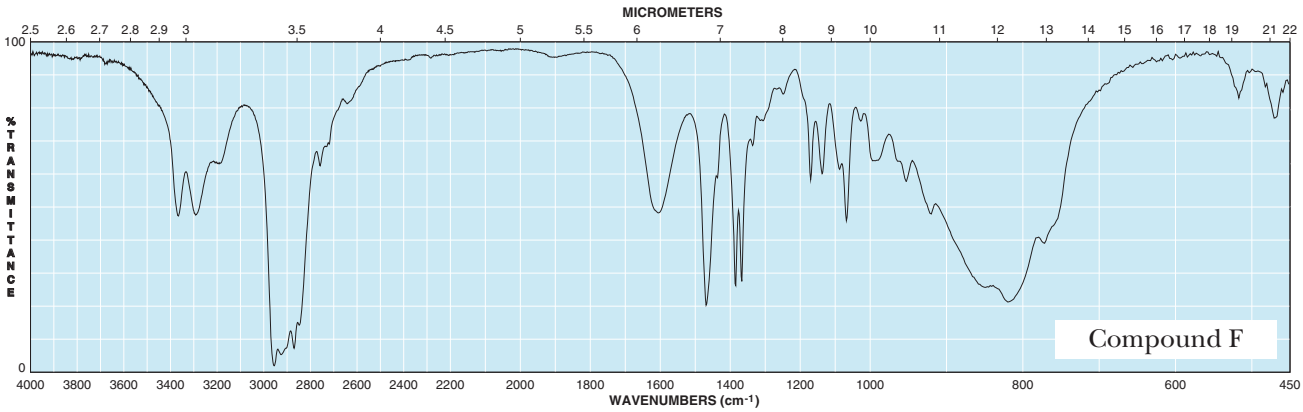


11.25 Examine the following IR spectrum and the molecular formula of compound F, $C_5H_{13}N$: Tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound F.

(c) The nitrogen-containing functional group(s) compound F might contain.

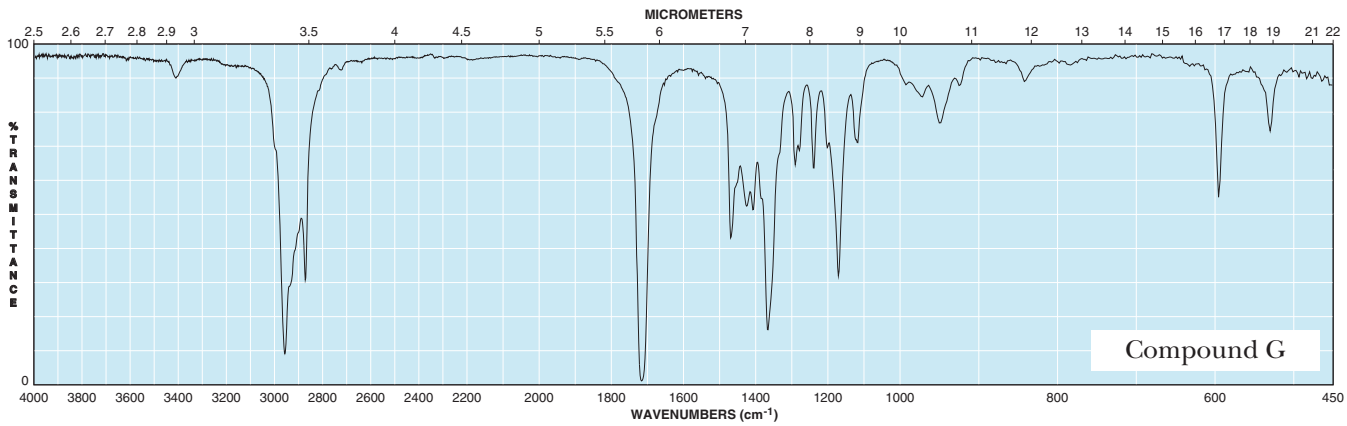


11.26 Examine the following IR spectrum and the molecular formula of compound G, $C_6H_{12}O$: Tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound G.

(c) What structural features would account for this IHD.

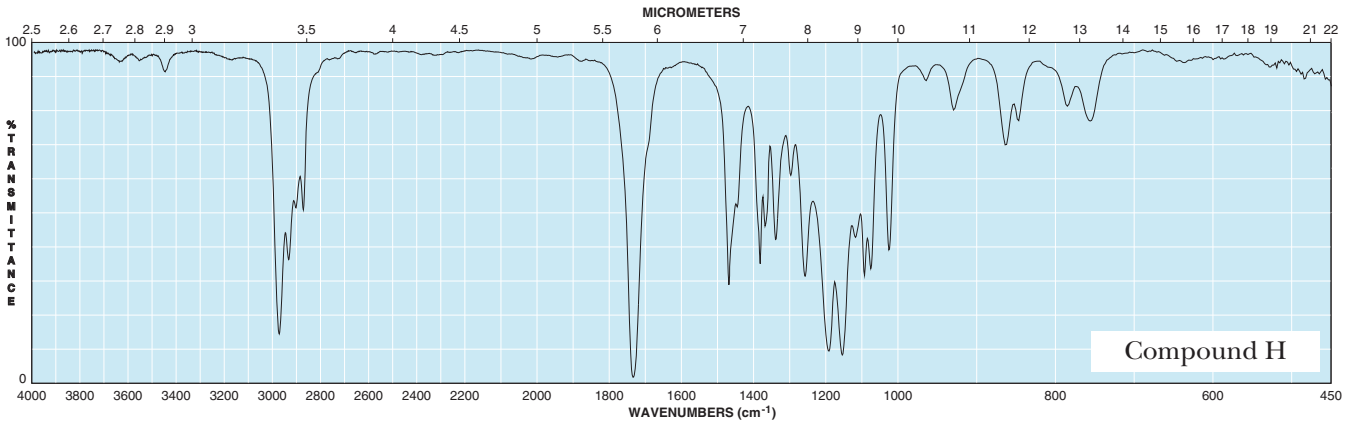


11.27 Examine the following IR spectrum and the molecular formula of compound H, $C_6H_{12}O_2$: Tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound H.

(c) The oxygen-containing functional group(s) compound H might contain.

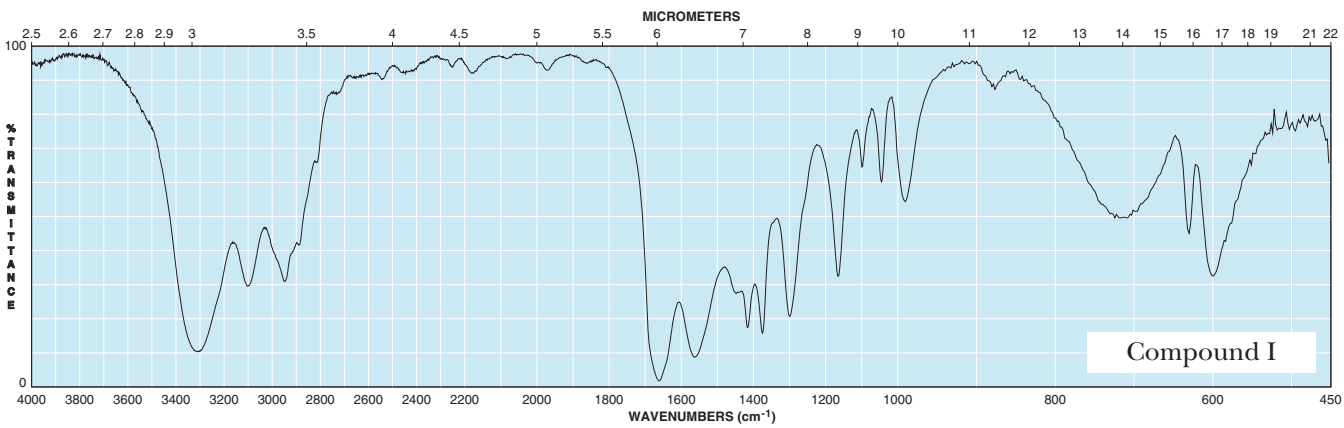


11.28 Examine the following IR spectrum and the molecular formula of compound I, C_3H_7NO: Tell **(See Examples 11.4–11.7)**

(a) Its IHD.

(b) The number of rings or pi bonds (or both) in compound I.

(c) The oxygen- and nitrogen-containing functional group(s) in compound I.



11.29 Show how IR spectroscopy can be used to distinguish between the compounds in each of the following pairs: **(See Examples 11.2, 11.3)**

(a) 1-Butanol and diethyl ether

(b) Butanoic acid and 1-butanol

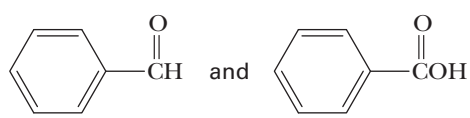
(c) Butanoic acid and 2-butanone

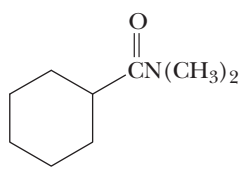
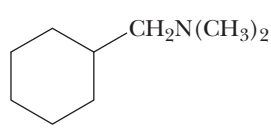
(d) Butanal and 1-butene

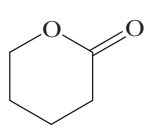
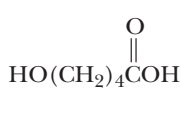
(e) 2-Butanone and 2-butanol

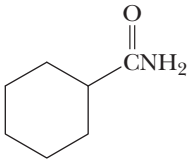
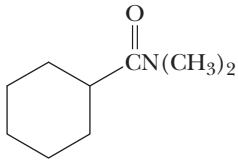
(f) Butane and 2-butene

11.30 For each pair of compounds that follows, list one major feature that appears in the IR spectrum of one compound, but not the other. In your answer, state what type of bond vibration is responsible for the spectral feature you list, and give its approximate position in the IR spectrum. **(See Examples 11.2, 11.3)**

(a)  and

(b)  and 

(c)  and 

(d)  and 

(e) $CH_3C{\equiv}CH$ and $CH_3C{\equiv}CCH_3$

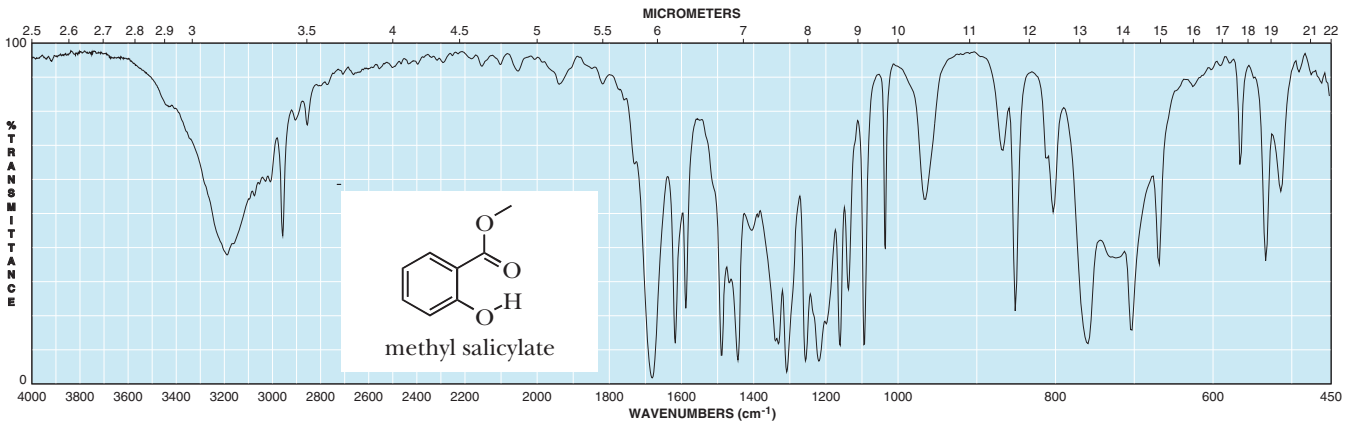
***11.31** Following are an infrared spectrum and a structural formula for methyl salicylate, the fragrant component of oil of wintergreen. On this spectrum, locate the absorption peak(s) due to **(See Examples 11.2, 11.3)**

(a) O—H stretching of the hydrogen-bonded —OH group (very broad and of medium intensity).

(b) C—H stretching of the aromatic ring (sharp and of weak intensity).

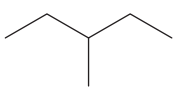
(c) C═O stretching of the ester group (sharp and of strong intensity).

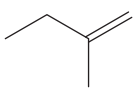
(d) C═C stretching of the aromatic ring (sharp and of medium intensity).

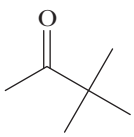


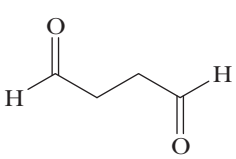
SECTION 11.8 Equivalency of Hydrogens and Carbons

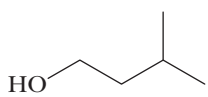
11.32 Determine the number of signals you would expect to see in the ^{1}H-NMR spectrum of each of the following compounds. **(See Examples 11.9, 11.13)**

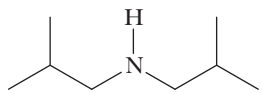
(a) 

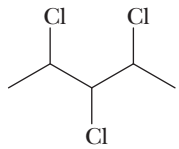
(b) 

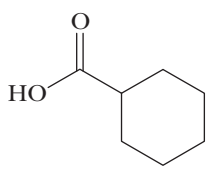
(c) 

(d) 

(e) 

(f) 

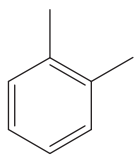
(g) 

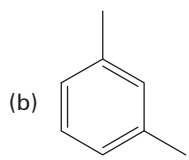
(h) 

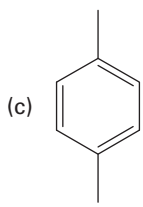
11.33 Determine the number of signals you would expect to see in the ^{13}C-NMR spectrum of each of the compounds in Problem 11.32. **(See Example 11.14)**

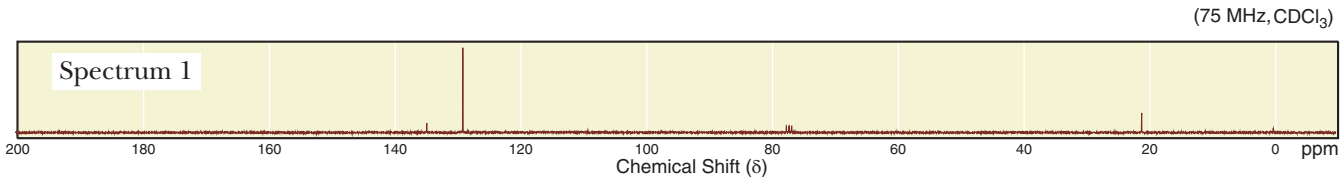
SECTION 11.13 Interpreting ^{1}H-NMR and ^{13}C-NMR Spectra

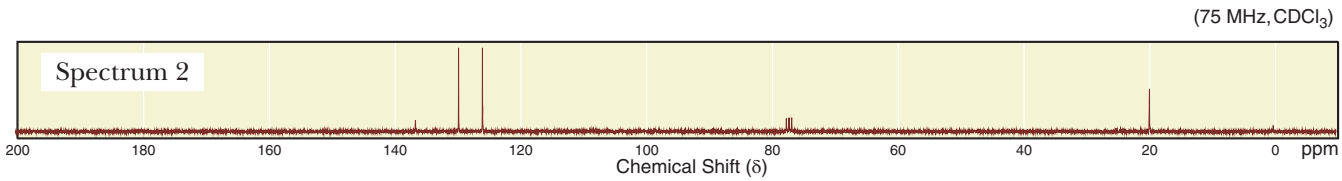
11.34 Following are structural formulas for the constitutional isomers of xylene and three sets of ^{13}C-NMR spectra. Assign each constitutional isomer its correct spectrum. **(See Example 11.17)**

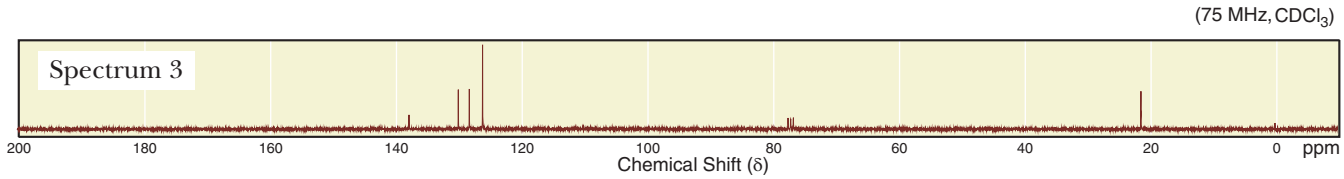
(a) 

(b) 

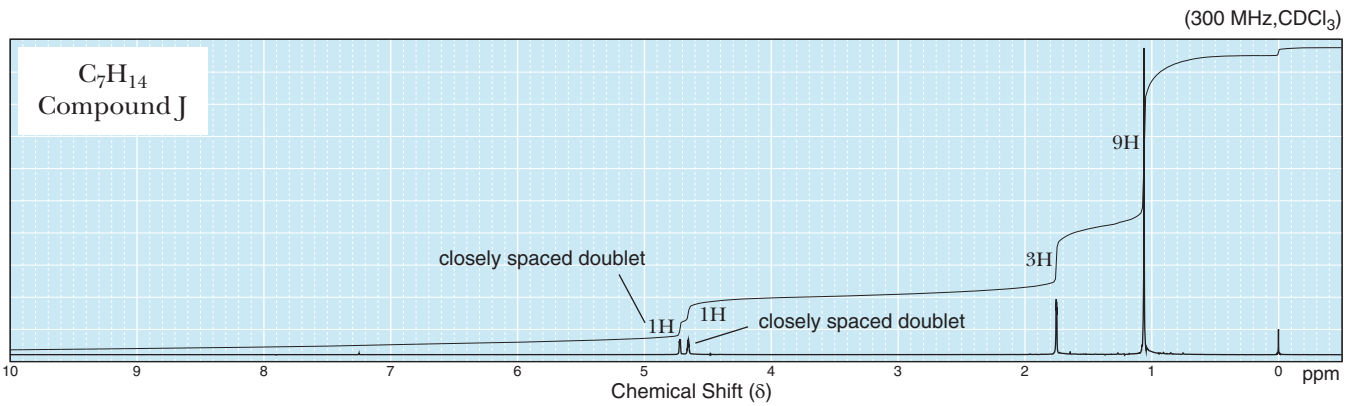
(c) 



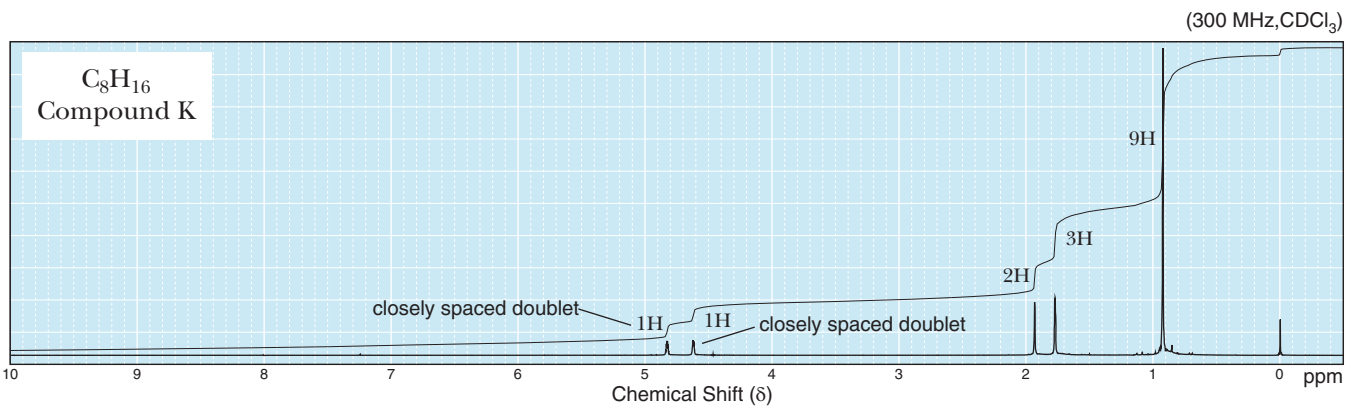




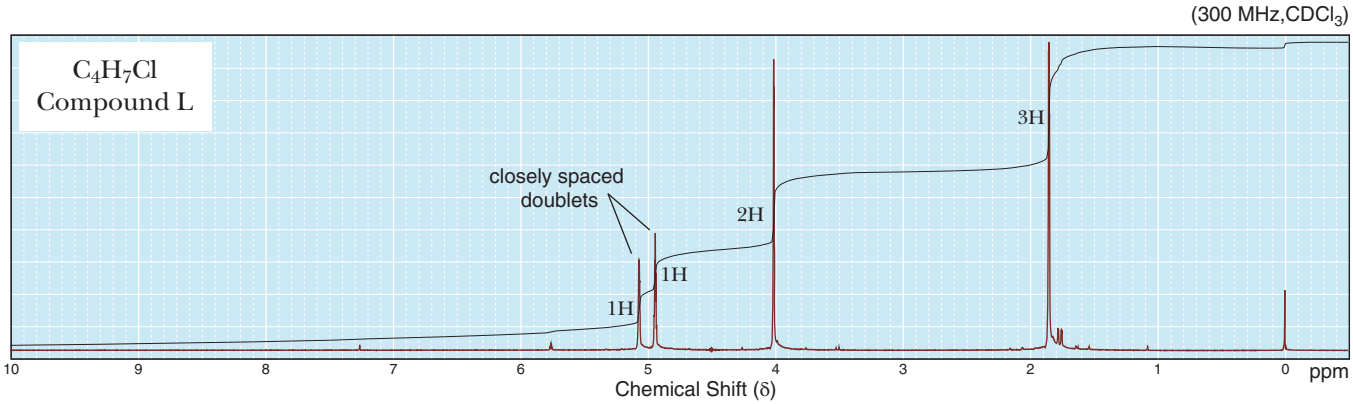
11.35 Following is a ^{1}H-NMR spectrum for compound J, with the molecular formula C_7H_{14}. Compound J decolorizes a solution of bromine in carbon tetrachloride. Propose a structural formula for compound J. **(See Examples 11.15, 11.16)**

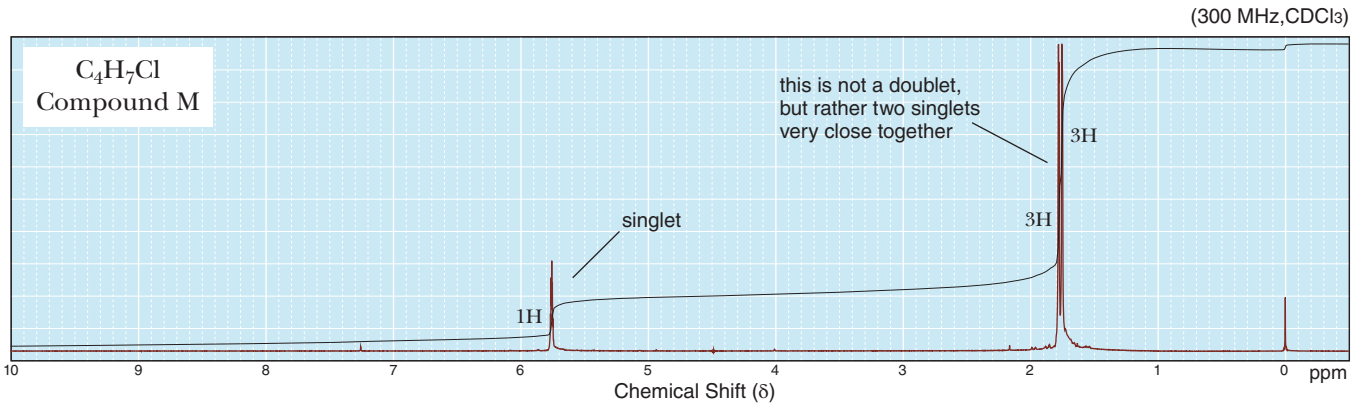


11.36 Following is a ^{1}H-NMR spectrum for compound K, with the molecular formula C_8H_{16}. Compound K decolorizes a solution of Br_2 in CCl_4. Propose a structural formula for compound K. **(See Examples 11.15, 11.16)**



11.37 Following are the ^{1}H-NMR spectra of compounds L and M, each with the molecular formula C_4H_7Cl. Each compound decolorizes a solution of Br_2 in CCl_4. Propose structural formulas for compounds L and M. **(See Examples 11.15, 11.16)**





11.38 Following are the structural formulas of three alcohols with the molecular formula $C_7H_{16}O$ and three sets of ^{13}C-NMR spectral data. Assign each constitutional isomer to its correct spectral data. **(See Example 11.17)**

(a) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH$

(b) $CH_3\overset{\displaystyle OH}{\overset{|}{C}}(CH_3)CH_2CH_2CH_2CH_3$

(c) $CH_3CH_2\overset{\displaystyle OH}{\overset{|}{C}}(CH_2CH_3)CH_2CH_3$

Spectrum 1	Spectrum 2	Spectrum 3
74.66	70.97	62.93
30.54	43.74	32.79
7.73	29.21	31.86
	26.60	29.14
	23.27	25.75
	14.09	22.63
		14.08

11.39 Alcohol N, with the molecular formula $C_6H_{14}O$, undergoes acid-catalyzed dehydration when it is warmed with phosphoric acid, giving compound O, with the molecular formula C_6H_{12}, as the major product. A ^{1}H-NMR spectrum of compound N shows peaks at δ 0.89 (t, 6H), 1.12 (s, 3H), 1.38 (s, 1H), and 1.48 (q, 4H). The ^{13}C-NMR spectrum of compound N shows peaks at δ 72.98, 33.72, 25.85, and 8.16. Propose structural formulas for compounds N and O. **(See Examples 11.15–11.17)**

11.40 Compound P, $C_6H_{14}O$, does not react with sodium metal and does not discharge the color of Br_2 in CCl_4. The ^{1}H-NMR spectrum of compound P consists of only two signals: a 12H doublet at δ 1.1 and a 2H septet at δ 3.6. Propose a structural formula for compound P. **(See Examples 11.15, 11.16)**

11.41 Propose a structural formula for each haloalkane: **(See Examples 11.15, 11.16)**

(a) $C_2H_4Br_2$ δ 2.5 (d, 3H) and 5.9 (q, 1H)

(b) $C_4H_8Cl_2$ δ 1.67 (d, 6H) and 2.15 (q, 2H)

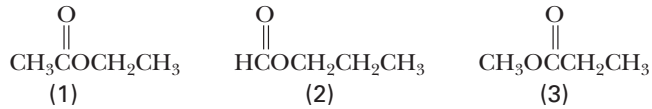
(c) $C_5H_8Br_4$ δ 3.6 (s, 8H)

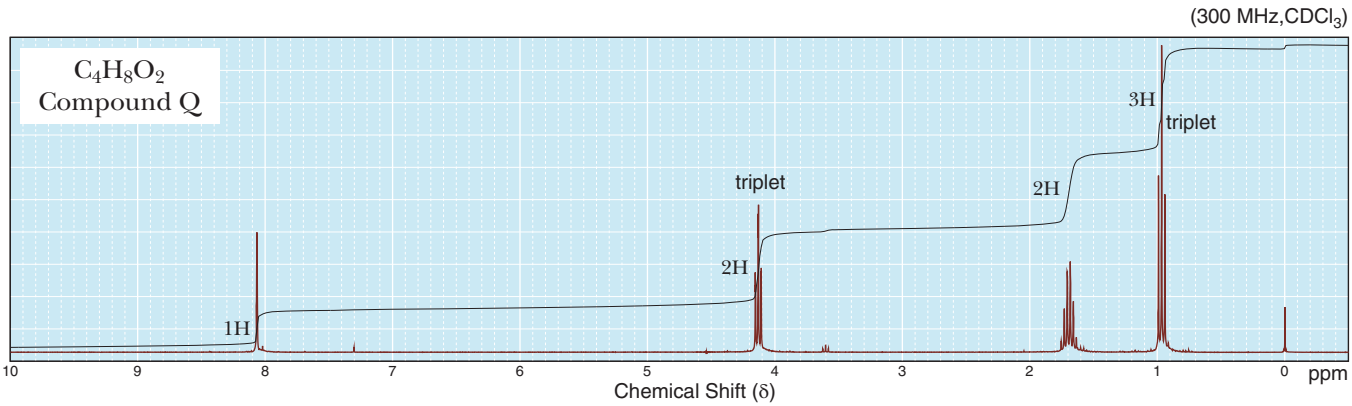
(d) C_4H_9Br δ 1.1 (d, 6H), 1.9 (m, 1H), and 3.4 (d, 2H)

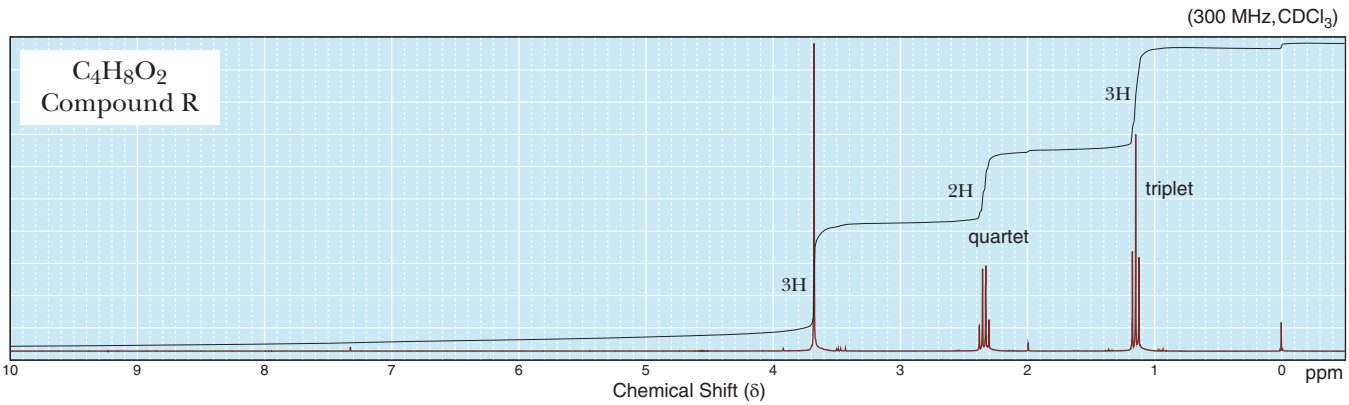
(e) $C_5H_{11}Br$ δ 1.1 (s, 9H) and 3.2 (s, 2H)

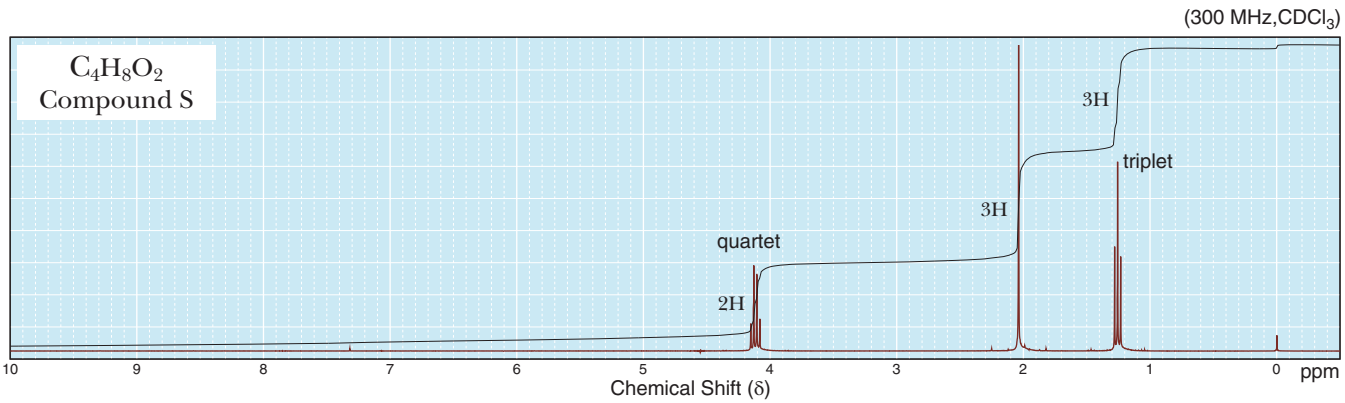
(f) $C_7H_{15}Cl$ δ 1.1 (s, 9H) and 1.6 (s, 6H)

11.42 Following are structural formulas for esters (1), (2), and (3) and three ^{1}H-NMR spectra. Assign each compound its correct spectrum (Q, R, or S) and assign all signals to their corresponding hydrogens. **(See Examples 11.15, 11.16)**



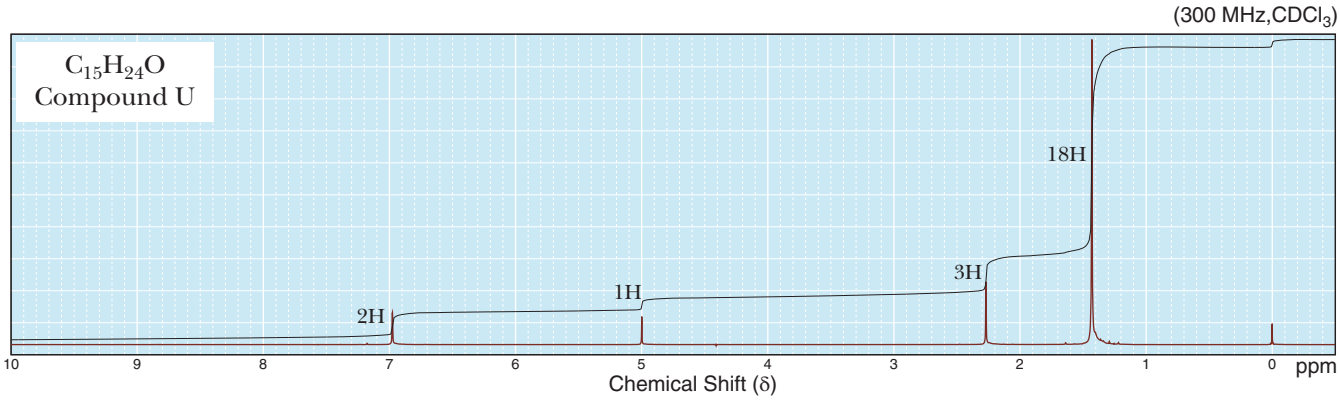


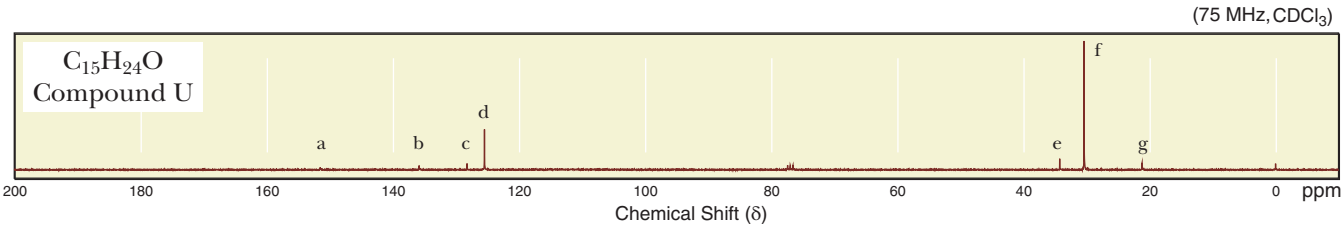




11.43 Compound T, $C_{10}H_{10}O_2$, is insoluble in water, 10% NaOH, and 10% HCl. A ^{1}H-NMR spectrum of compound T shows signals at δ 2.55 (s, 6H) and 7.97 (s, 4H). A ^{13}C-NMR spectrum of compound T shows four signals. From this information, propose a structural formula for T. **(See Examples 11.15–11.17)**

11.44 Compound U, $C_{15}H_{24}O$, is used as an antioxidant in many commercial food products, synthetic rubbers, and petroleum products. Propose a structural formula for compound U based on its ^{1}H-NMR and ^{13}C-NMR spectra. **(See Examples 11.15–11.17)**





11.45 Propose a structural formula for these compounds, each of which contains an aromatic ring: **(See Examples 11.15, 11.16)**

(a) $C_9H_{10}O$ δ 1.2 (t, 3H), 3.0 (q, 2H), and 7.4–8.0 (m, 5H)

(b) $C_{10}H_{12}O_2$ δ 2.2 (s, 3H), 2.9 (t, 2H), 4.3 (t, 2H), and 7.3 (s, 5H)

(c) $C_{10}H_{14}$ δ 1.2 (d, 6H), 2.3 (s, 3H), 2.9 (septet, 1H), and 7.0 (s, 4H)

(d) C_8H_9Br δ 1.8 (d, 3H), 5.0 (q, 1H), and 7.3 (s, 5H)

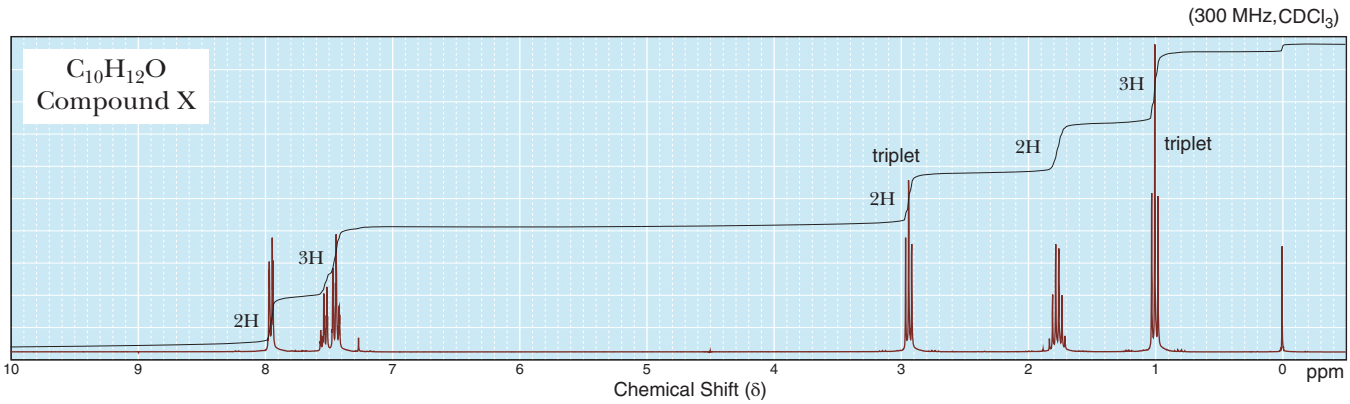
11.46 Compound V, with the molecular formula $C_9H_{12}O$, readily undergoes acid-catalyzed dehydration to give compound W, with the molecular formula C_9H_{10}. A ^{1}H-NMR spectrum of compound V shows signals at δ 0.91 (t, 3H), 1.78 (m, 2H), 2.26 (s, 1H), 4.55 (t, 1H), and 7.31 (m, 5H). From this information, propose structural formulas for compounds V and W. **(See Examples 11.15, 11.16)**

11.47 Propose a structural formula for each ketone: **(See Examples 11.15, 11.16)**

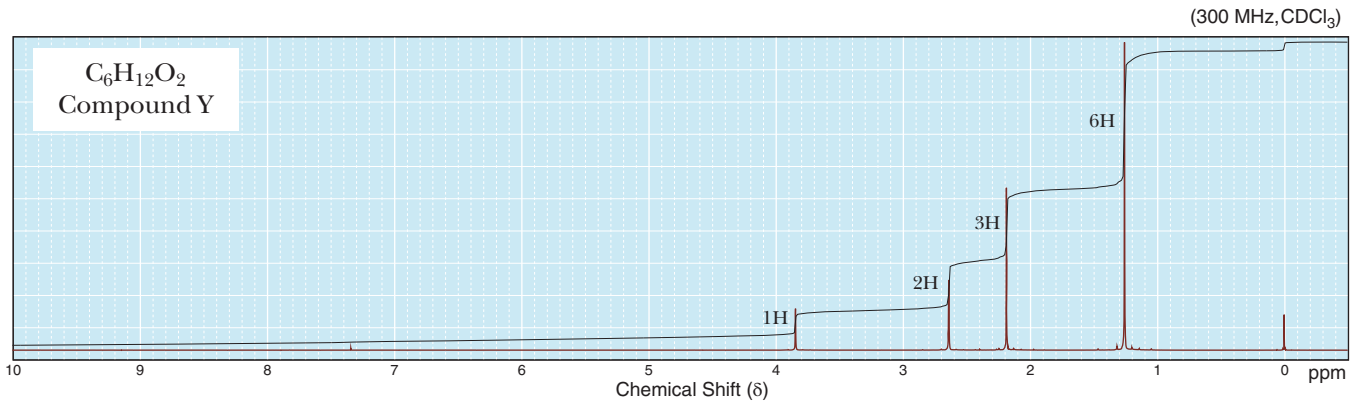
(a) C_4H_8O δ 1.0 (t, 3H), 2.1 (s 3H), and 2.4 (q, 2H)

(b) $C_7H_{14}O$ δ 0.9 (t, 6H), 1.6 (sextet, 4H), and 2.4 (t, 4H)

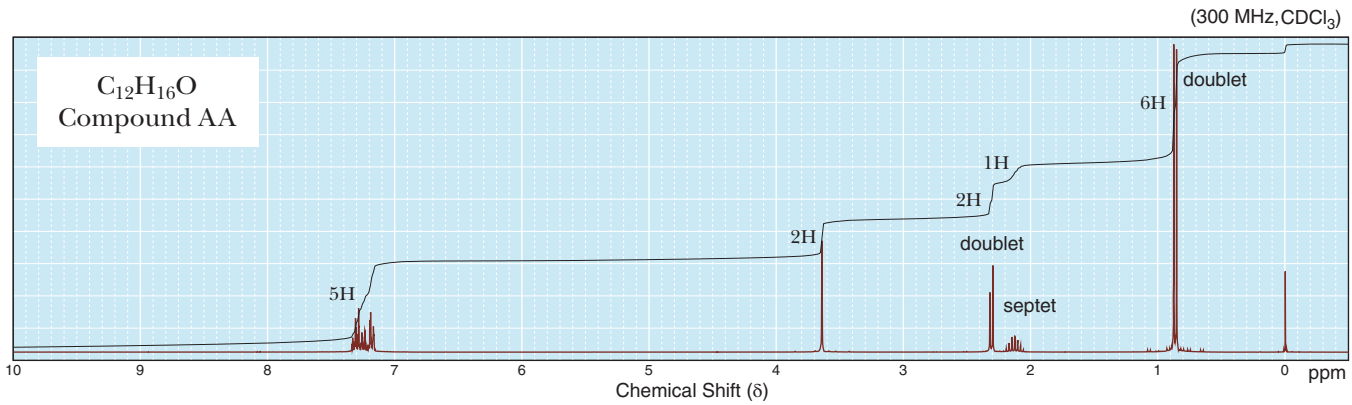
11.48 Propose a structural formula for compound X, a ketone with the molecular formula $C_{10}H_{12}O$: **(See Examples 11.15, 11.16)**

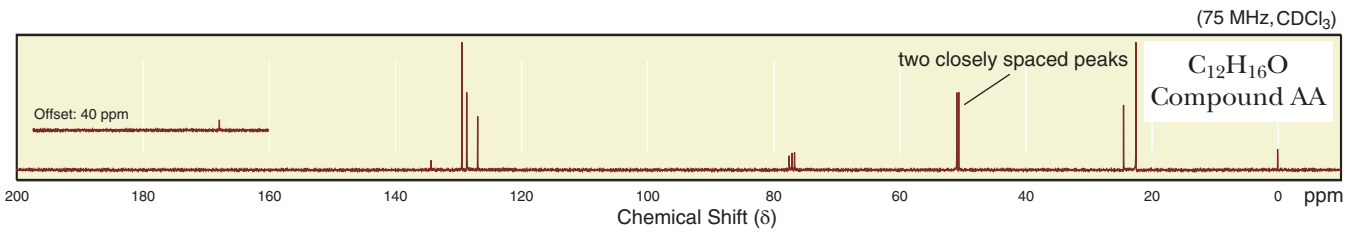


11.49 Following is a ^{1}H-NMR spectrum for compound Y, with the molecular formula $C_6H_{12}O_2$. Compound Y undergoes acid-catalyzed dehydration to give compound Z, $C_6H_{10}O$. Propose structural formulas for compounds Y and Z. **(See Examples 11.15, 11.16)**



11.50 Propose a structural formula for compound AA, with the molecular formula $C_{12}H_{16}O$. Following are its ^{1}H-NMR and ^{13}C-NMR spectra: **(See Examples 11.15–11.17)**





11.51 Propose a structural formula for each carboxylic acid: **(See Examples 11.15–11.17)**

(a) $C_5H_{10}O_2$

^{1}H-NMR	^{13}C-NMR
0.94 (t, 3H)	180.7
1.39 (m, 2H)	33.89
1.62 (m, 2H)	26.76
2.35 (t, 2H)	22.21
12.0 (s, 1H)	13.69

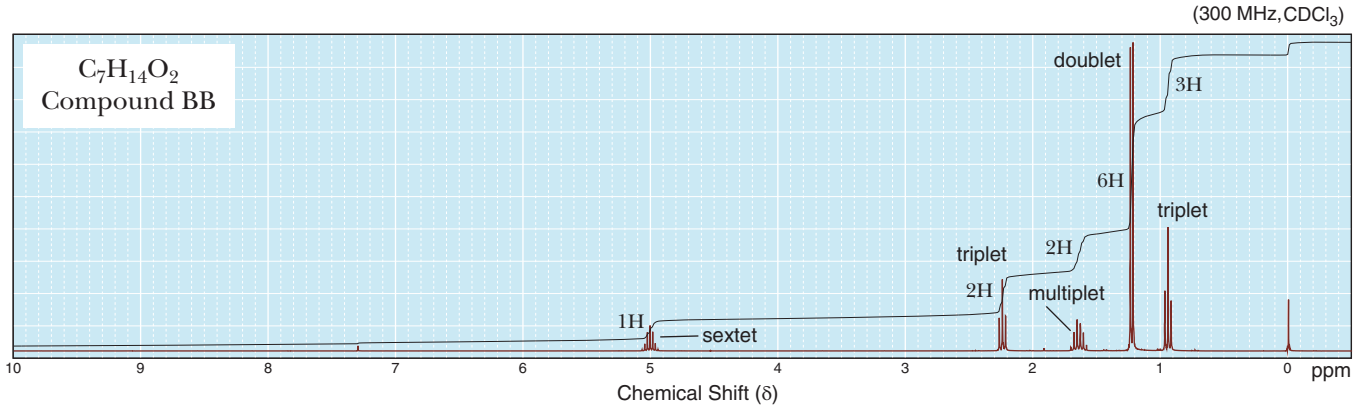
(b) $C_6H_{12}O_2$

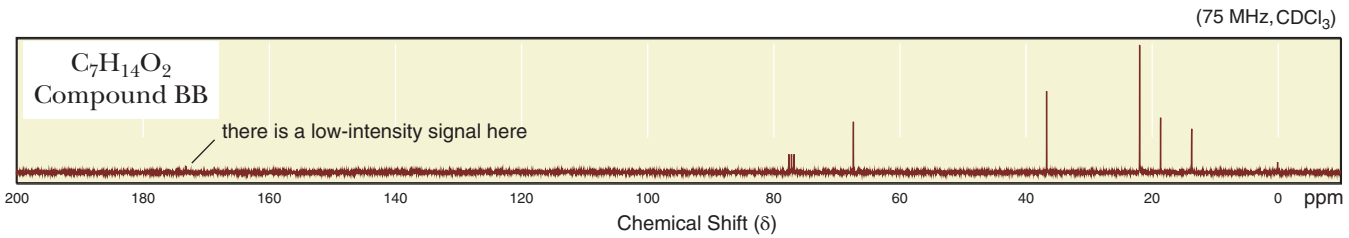
^{1}H-NMR	^{13}C-NMR
1.08 (s, 9H)	179.29
2.23 (s, 2H)	46.82
12.1 (s, 1H)	30.62
	29.57

(c) $C_5H_8O_4$

^{1}H-NMR	^{13}C-NMR
0.93 (t, 3H)	170.94
1.80 (m, 2H)	53.28
3.10 (t, 1H)	21.90
12.7 (s, 2H)	11.81

11.52 Following are ^{1}H-NMR and ^{13}C-NMR spectra of compound BB, with the molecular formula $C_7H_{14}O_2$. Propose a structural formula for compound BB. **(See Examples 11.15–11.17)**





11.53 Propose a structural formula for each ester: **(See Examples 11.15–11.17)**

(a) $C_6H_{12}O_2$

^{1}H-NMR	^{13}C-NMR
1.18 (d, 6H)	177.16
1.26 (t, 3H)	60.17
2.51 (m, 1H)	34.04
4.13 (q, 2H)	19.01
	14.25

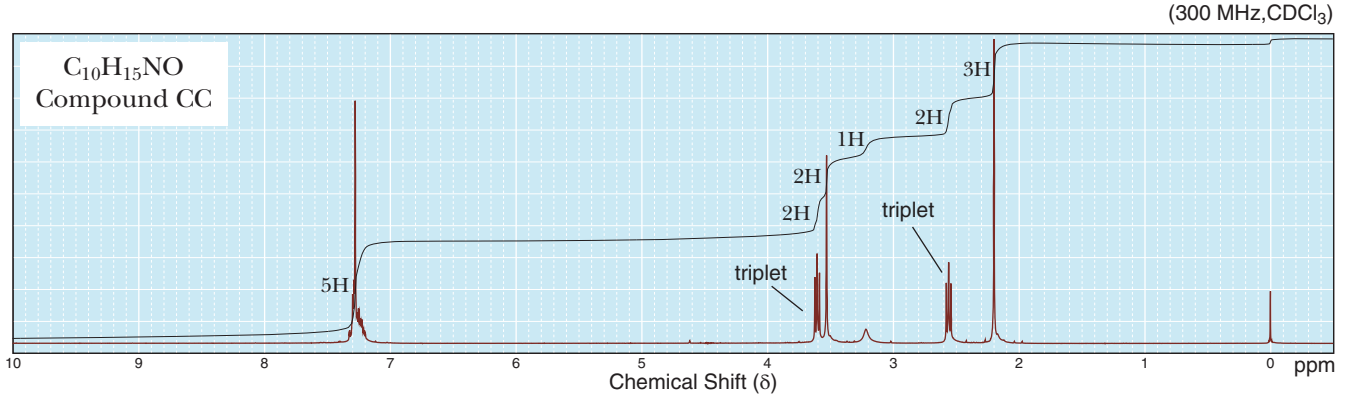
(b) $C_7H_{12}O_4$

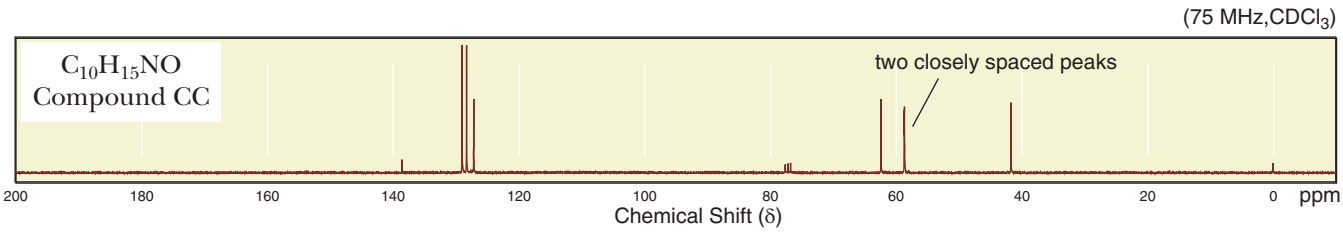
^{1}H-NMR	^{13}C-NMR
1.28 (t, 6H)	166.52
3.36 (s, 2H)	61.43
4.21 (q, 4H)	41.69
	14.07

(c) $C_7H_{14}O_2$

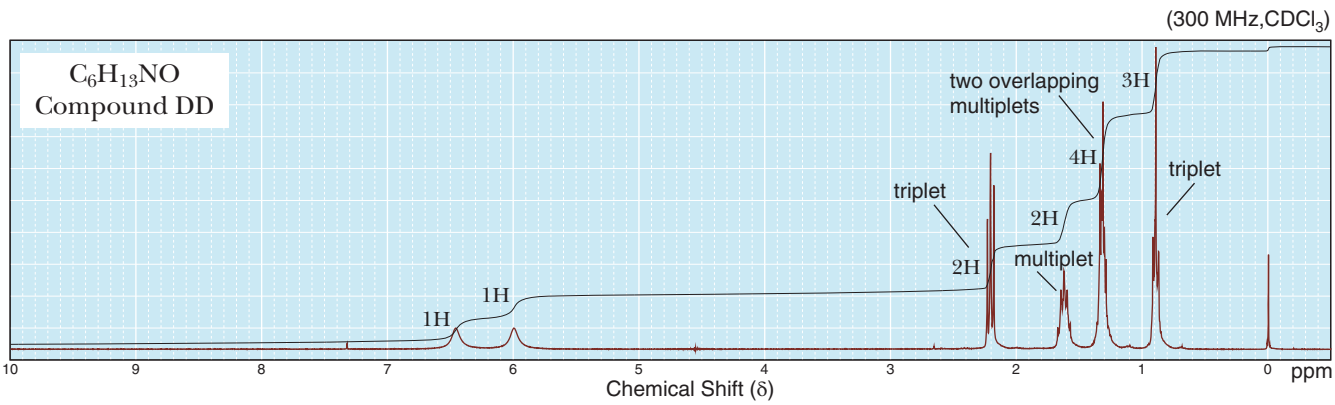
^{1}H-NMR	^{13}C-NMR
0.92 (d, 6H)	171.15
1.52 (m, 2H)	63.12
1.70 (m, 1H)	37.31
2.09 (s, 3H)	25.05
4.10 (t, 2H)	22.45
	21.06

11.54 Following are ^{1}H-NMR and ^{13}C-NMR spectra of compound CC, with the molecular formula $C_{10}H_{15}NO$. Propose a structural formula for this compound. **(See Examples 11.15–11.17)**

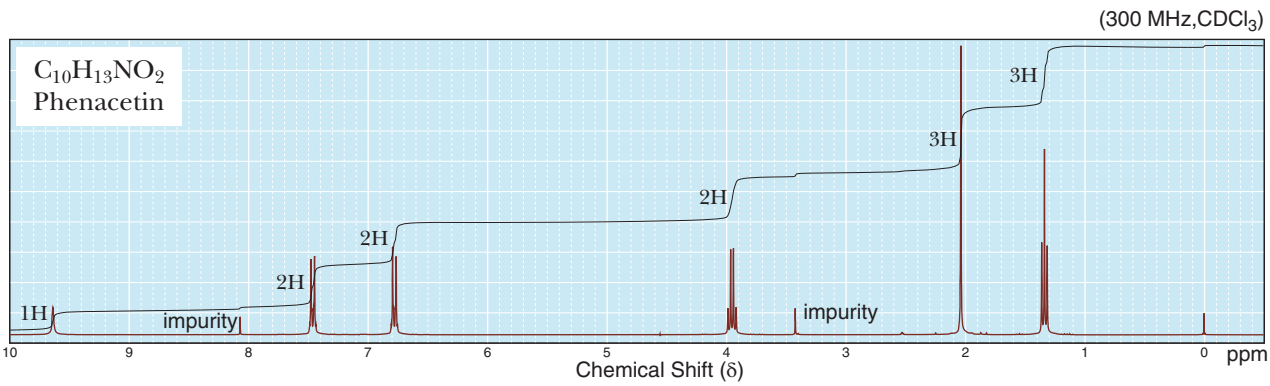




11.55 Propose a structural formula for amide DD, with the molecular formula $C_6H_{13}NO$: **(See Examples 11.15, 11.16)**

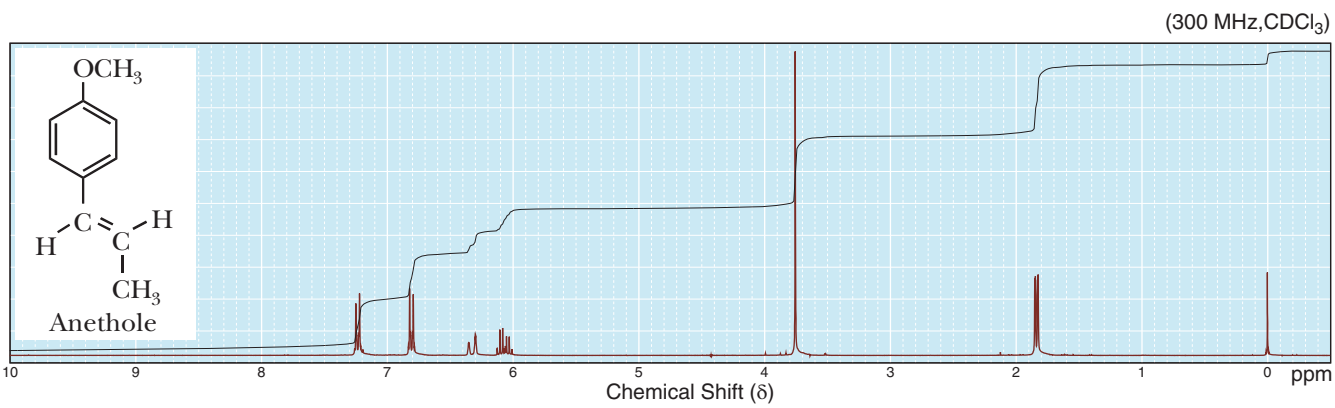


11.56 Propose a structural formula for the analgesic phenacetin, with molecular formula $C_{10}H_{13}NO_2$, based on its ^{1}H-NMR spectrum: **(See Examples 11.15, 11.16)**

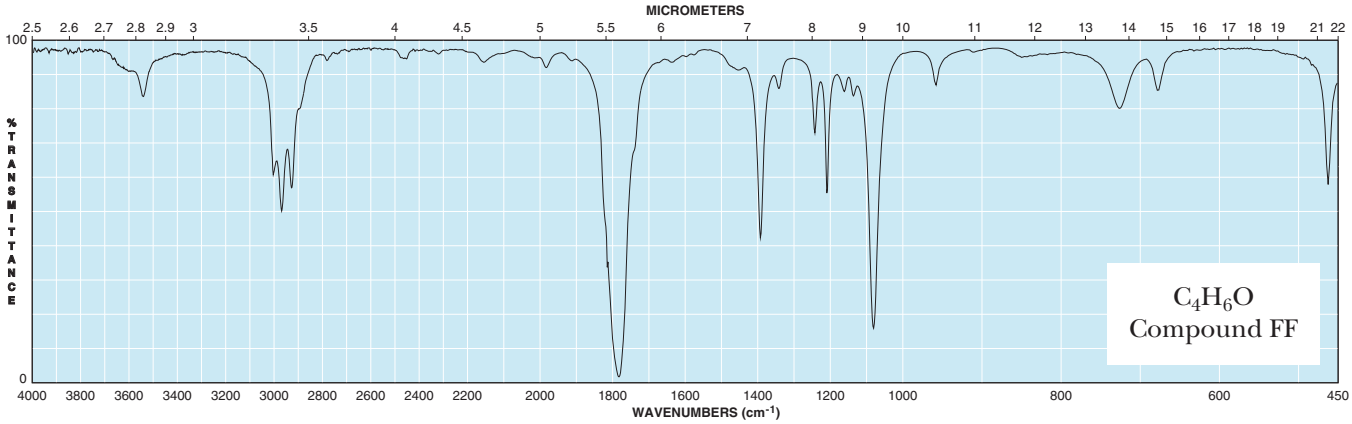


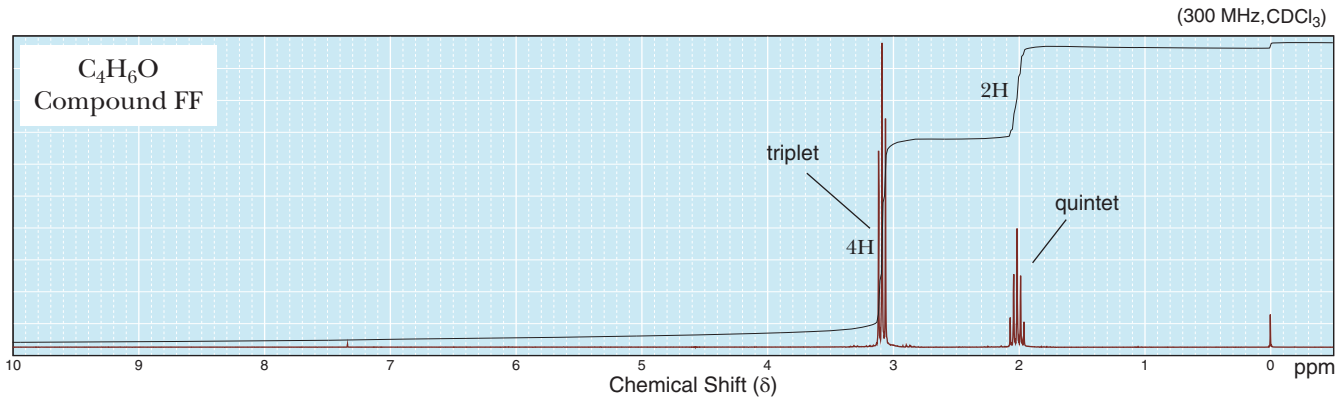
11.57 Propose a structural formula for compound EE, an oily liquid with the molecular formula $C_8H_9NO_2$. Compound EE is insoluble in water and aqueous NaOH, but dissolves in 10% HCl. When its solution in HCl is neutralized with NaOH, compound EE is recovered unchanged. A ^{1}H-NMR spectrum of compound EE shows signals at δ 3.84 (s, 3H), 4.18 (s, 2H), 7.60 (d, 2H), and 8.70 (d, 2H). **(See Examples 11.15, 11.16)**

11.58 Following is a ^{1}H-NMR spectrum and a structural formula for anethole, $C_{10}H_{12}O$, a fragrant natural product obtained from anise. Using the line of integration, determine the number of protons giving rise to each signal. Show that this spectrum is consistent with the structure of anethole. **(See Examples 11.15, 11.16)**

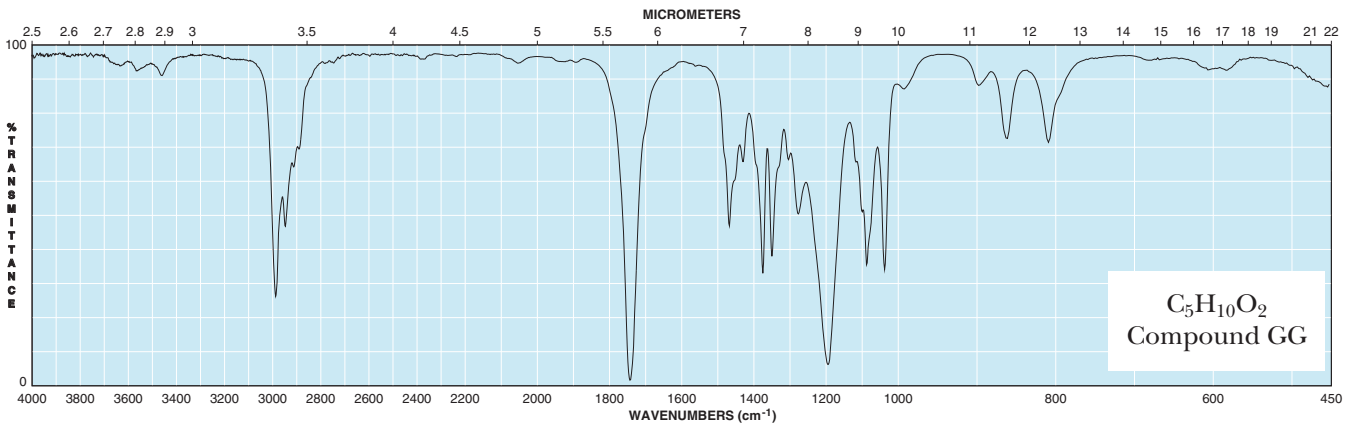


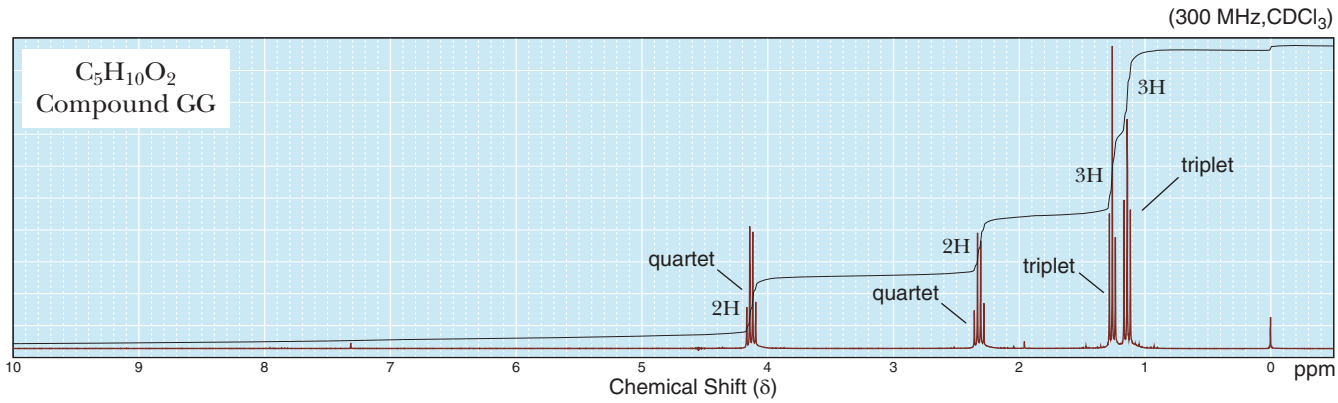
11.59 Propose a structural formula for compound FF, with the molecular formula C_4H_6O, based on the following IR and ^{1}H-NMR spectra: **(See Examples 11.15, 11.16)**



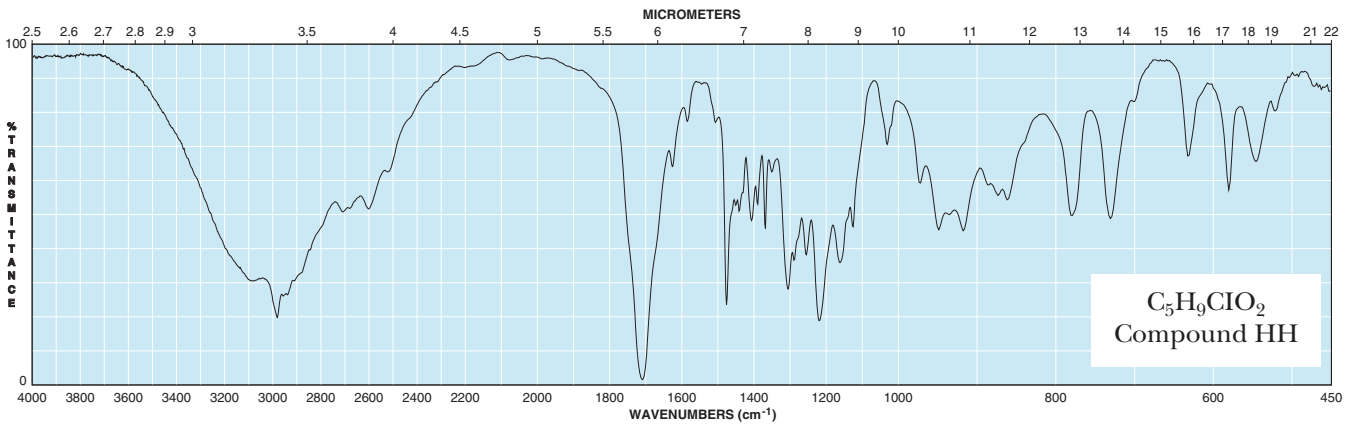


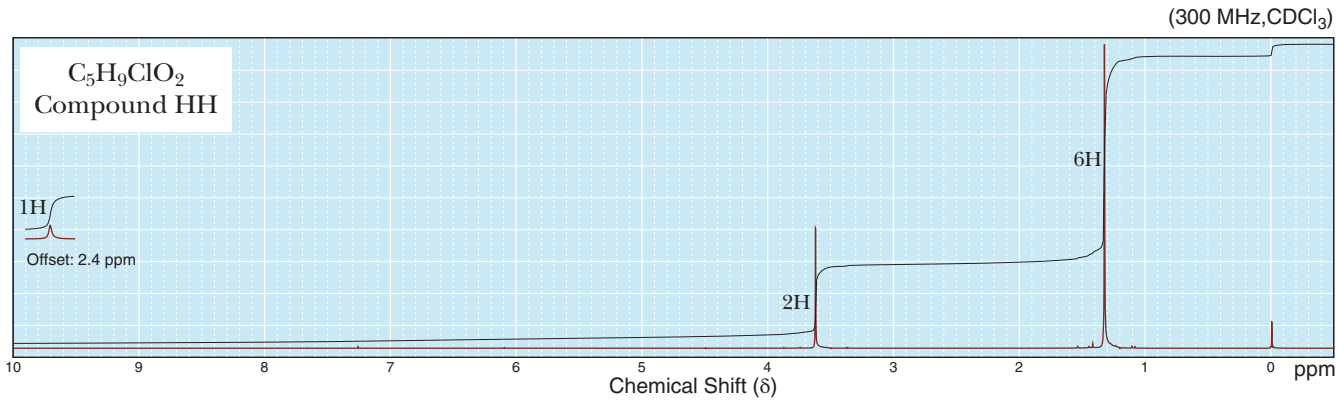
11.60 Propose a structural formula for compound GG, with the molecular formula $C_5H_{10}O_2$, based on the following IR and ^{1}H-NMR spectra: **(See Examples 11.15, 11.16)**



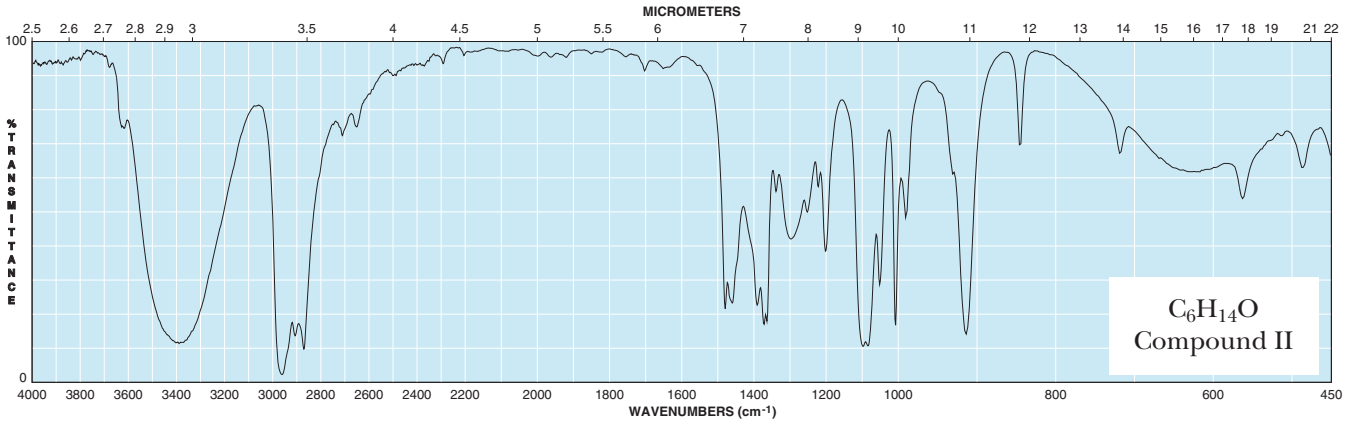


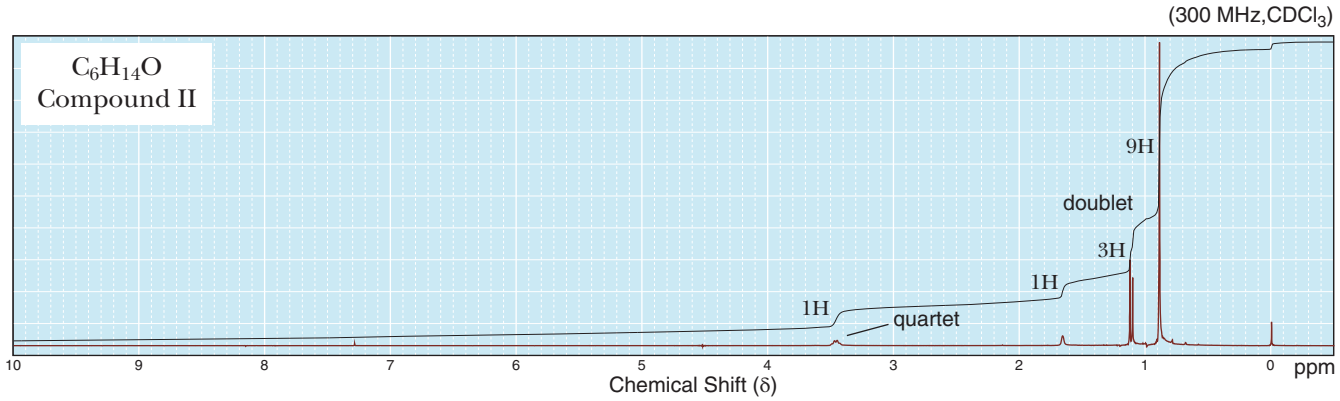
11.61 Propose a structural formula for compound HH, with the molecular formula $C_5H_9ClO_2$, based on the following IR and ^{1}H-NMR spectra: **(See Examples 11.15, 11.16)**





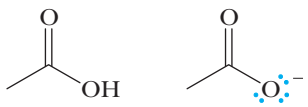
11.62 Propose a structural formula for compound II, with the molecular formula $C_6H_{14}O$, based on the following IR and ^{1}H-NMR spectra: **(See Examples 11.15, 11.16)**





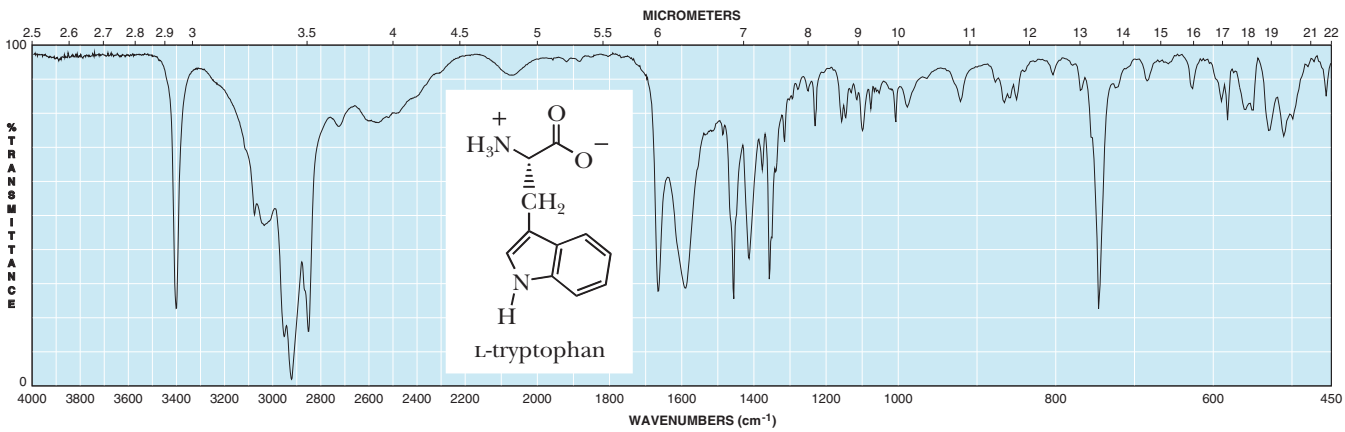
LOOKING AHEAD

11.63 Predict the position of the C═O stretching absorption in acetate ion relative to that in acetic acid:



Acetic acid Acetate ion

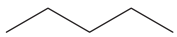
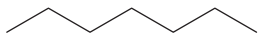
***11.64** Following is the IR spectrum of L-tryptophan, a naturally occurring amino acid that is abundant in foods such as turkey:

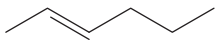


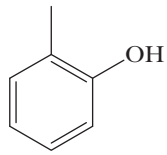
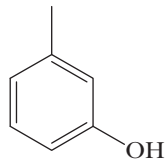
For many years, the L-tryptophan in turkey was believed to make people drowsy after Thanksgiving dinner. Scientists now know that consuming L-tryptophan makes one drowsy only if the compound is taken on an empty stomach. Therefore, it is unlikely that one's Thanksgiving Day turkey is the cause of drowsiness. Notice that L-tryptophan contains one stereocenter. Its enantiomer, D-tryptophan, does not occur in nature but can be synthesized in the laboratory. What would the IR spectrum of D-tryptophan look like?

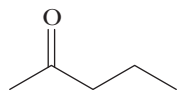
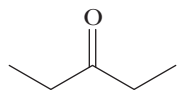
GROUP LEARNING ACTIVITIES

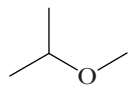
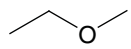
11.65 Discuss whether IR or NMR spectroscopy could be used to distinguish between the following pairs of molecules. Be very specific in describing the spectral data that would allow you to identify each compound. Assume that you do not have the reference spectra of either molecule.

(a)  and 

(b)  and 

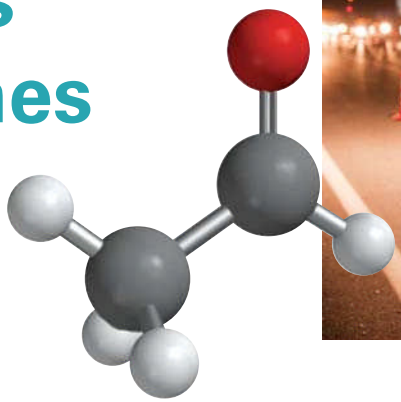
(c)  and 

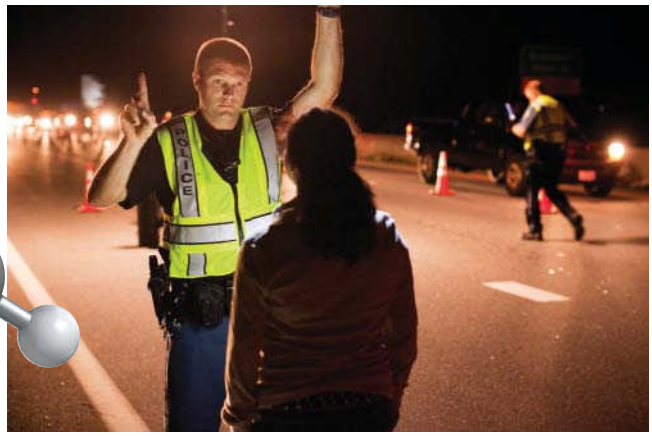
(d)  and 

(e)  and 

What Is an NMR Spectrum?

Aldehydes and Ketones



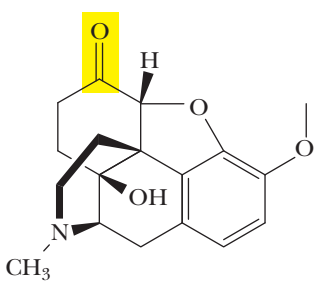


Carl D. Walsh/Portland Press Herald via/Getty Images, Inc.

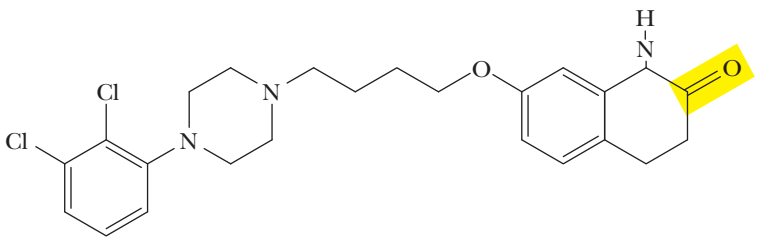
12

Ethanol from alcoholic beverages is first metabolized to acetaldehyde before being broken down further in the body. The reactivity of the carbonyl group of acetaldehyde allows it to bind to proteins in the body, the products of which lead to tissue damage and organ disease. Inset: A model of acetaldehyde.

OXYCODONE, AN ANALGESIC painkiller, and aripiprazole, an antipsychotic, are among two of the most prescribed drugs in the United States. Both contain the carbonyl group, C═O, the functional group of aldehydes and ketones (Chapter 12), and carboxylic acids (Chapter 13) and their derivatives (Chapter 14). The presence of carbonyls in so many compounds of biological and medical relevance make it one of the most important functional groups in chemistry and biochemistry. We begin our study of the physical and chemical properties of the carbonyl group with the ketones and aldehydes, two classes of compounds whose characteristic reaction themes lead very quickly to an understanding of a wide variety of organic reactions.



Oxycodone



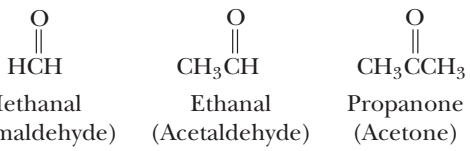
Aripiprazole

12.1 What Are Aldehydes and Ketones?

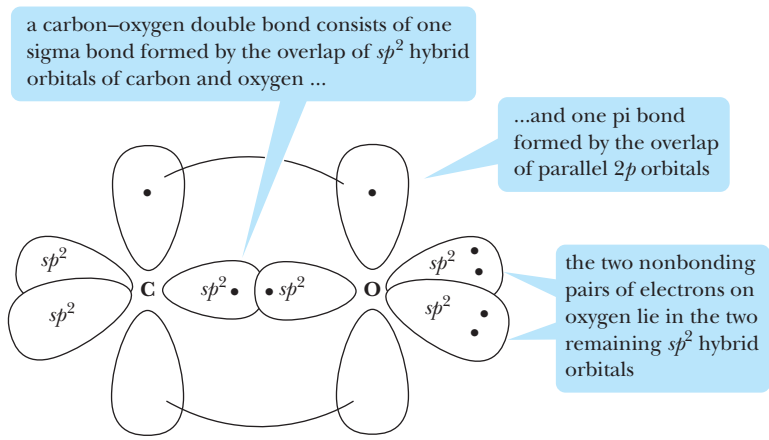
An **aldehyde** is a carbonyl group bonded to a hydrogen atom (Section 1.7C). In methanal (common name: formaldehyde), the simplest aldehyde, the carbonyl group is bonded to two hydrogen atoms. In other aldehydes, it is bonded to one hydrogen atom and one carbon atom. A **ketone** is a carbonyl group bonded to two carbon atoms (Section 1.7C). Following are Lewis structures for the aldehydes methanal and ethanal, and a Lewis structure for propanone, the simplest ketone. Under each in parentheses is its common name:

Aldehyde A compound containing a carbonyl group bonded to hydrogen (a —CHO group).

Ketone A compound containing a carbonyl group bonded to two carbons.



Methanal (Formaldehyde) | Ethanal (Acetaldehyde) | Propanone (Acetone)

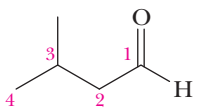


12.2 How Are Aldehydes and Ketones Named?

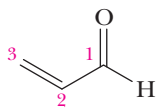
A. IUPAC Nomenclature

The IUPAC system of nomenclature for aldehydes and ketones follows the familiar pattern of selecting the longest chain of carbon atoms that contains the functional group as the parent alkane. We show the aldehyde group by changing the suffix *-e* of the parent alkane to *-al*, as in methanal (Section 3.5). Because the carbonyl group of an aldehyde can appear only at the end of a parent chain and numbering must start with that group as carbon-1, its position is unambiguous; there is no need to use a number to locate it.

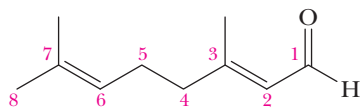
For **unsaturated aldehydes**, the presence of a carbon–carbon double bond is indicated by the infix *-en-*. As with other molecules with both an infix and a suffix, the location of the suffix determines the numbering pattern.



3-Methylbutanal



2-Propenal (Acrolein)

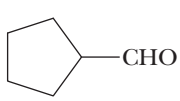


(2*E*)-3,7-Dimethyl-2,6-octadienal (Geranial)

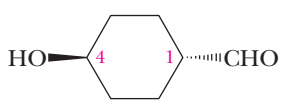
© rakratchada torsap/Alamy StockPhoto

Geranial is present in the oil of lemongrass and helps give some soups their lemon flavour.

For cyclic molecules in which —CHO is bonded directly to the ring, we name the molecule by adding the suffix *-carbaldehyde* to the name of the ring. We number the atom of the ring bearing the aldehyde group as number 1:



Cyclopentanecarbaldehyde



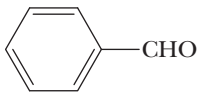
trans-4-Hydroxycyclohexanecarbaldehyde

Among the aldehydes for which the IUPAC system retains common names are benzaldehyde and cinnamaldehyde. Note here the alternative ways of writing the phenyl group.

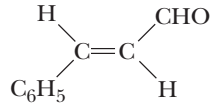
Thomas Poon

Dihydroxyacetone is the active ingredient in several artificial tanning preparations.

In benzaldehyde it is written as a line-angle formula, and in cinnamaldehyde it is abbreviated C_6H_5—.



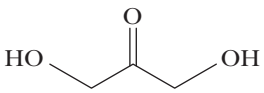
Benzaldehyde



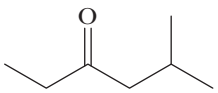
trans-3-Phenyl-2-propenal (Cinnamaldehyde)

Two other aldehydes whose common names are retained in the IUPAC system are formaldehyde and acetaldehyde.

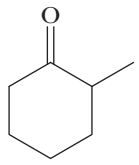
In the IUPAC system, we name ketones by selecting the longest chain that contains the carbonyl group and making that chain the parent alkane. We indicate the presence of the ketone by changing the suffix from *-e* to *-one* (Section 3.5). We number the parent chain from the direction that gives the carbonyl carbon the smaller number. The IUPAC system retains the common names acetophenone and benzophenone:



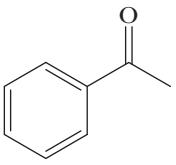
Dihydroxyacetone



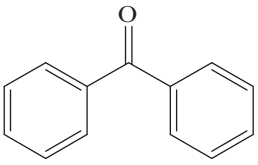
5-Methyl-3-hexanone



2-Methyl-cyclohexanone



Acetophenone

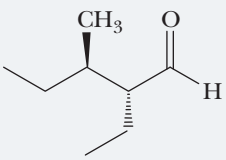


Benzophenone

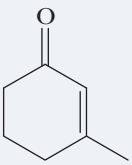
EXAMPLE 12.1

Write the IUPAC name for each compound:

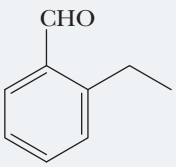
(a)



(b)



(c)



STRATEGY

First determine the root name from the longest chain of carbons that contains the carbonyl group. If the carbonyl is an aldehyde, the suffix will be *-al*. If the carbonyl is a ketone, the suffix will be *-one*. Then identify the atoms or groups of atoms that are not part of that chain of carbons. These are your substituents. If the root name indicates a ring and an aldehyde is bonded to the ring, the suffix *-carbaldehyde* is used. Finally, remember that certain aldehydes and ketones retain their common names in the IUPAC system.

SOLUTION

(a) The longest chain has six carbons, but the longest chain that contains the carbonyl group has five carbons. The IUPAC name of this compound is (2*R*,3*R*)-2-ethyl-3-methylpentanal.

(b) Number the six-membered ring beginning with the carbonyl carbon. The IUPAC name of this compound is 3-methyl-2-cyclohexenone.

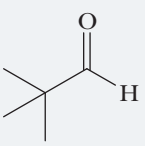
(c) This molecule is derived from benzaldehyde. Its IUPAC name is 2-ethylbenzaldehyde.

See problems 12.17, 12.18

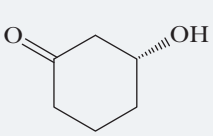
PROBLEM 12.1

Write the IUPAC name for each compound:

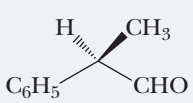
(a)



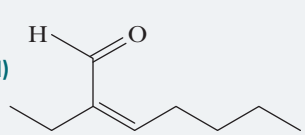
(b)



(c)



(d)



EXAMPLE 12.2

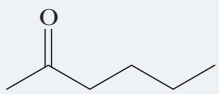
Write structural formulas for all ketones with the molecular formula $C_6H_{12}O$, and give each its IUPAC name. Which of these ketones are chiral?

STRATEGY

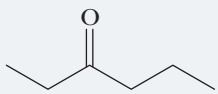
Start with an unbranched carbon skeleton. Place the carbonyl group, one at a time, at each position (except carbon-1). Next, consider branching possibilities, and repeat the process of placing the carbonyl at different positions. A ketone will be chiral if it has one stereocenter or if it has two or more stereocenters and is not superposable on its mirror image.

SOLUTION

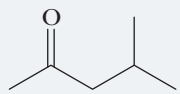
Following are line-angle formulas and IUPAC names for the six ketones with the given molecular formula:



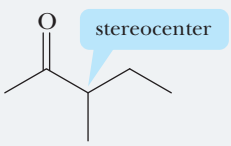
2-Hexanone



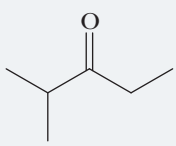
3-Hexanone



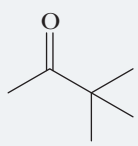
4-Methyl-2-pentanone



3-Methyl-2-pentanone



2-Methyl-3-pentanone



3,3-Dimethyl-2-butanone

Only 3-methyl-2-pentanone has a stereocenter and is chiral.

See problems 12.15, 12.16

PROBLEM 12.2

Write structural formulas for all aldehydes with molecular formula $C_6H_{12}O$, and give each its IUPAC name. Which of these aldehydes are chiral?

B. IUPAC Names for More Complex Aldehydes and Ketones

In naming compounds that contain more than one functional group, the IUPAC has established an **order of precedence of functional groups**. Table 12.1 gives the order of precedence for the functional groups we have studied so far.

Order of precedence of functional groups A system for ranking functional groups in order of priority for the purposes of IUPAC nomenclature.

C. Common Names

The common name for an aldehyde is derived from the common name of the corresponding carboxylic acid by dropping the word *acid* and changing the suffix *-ic* or *-oic* to *-aldehyde*. Because we have not yet studied common names for carboxylic acids, we are not in a position to discuss common names for aldehydes. We can, however, illustrate how they are derived by reference to two common names of carboxylic acids with which you are familiar. The name formaldehyde is derived from formic acid, and the name acetaldehyde from acetic acid:

Formaldehyde

Formic acid

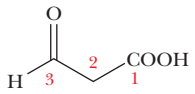
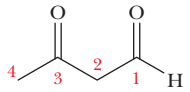
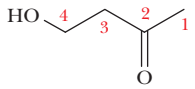
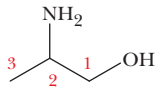
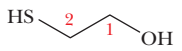
Acetaldehyde

Acetic acid

© Ashley Cooper/Alamy Stock Photo

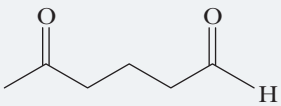
Formaldehyde was once used to embalm humans and preserve cadavers, but is now known to be a carcinogen.

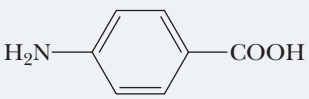
TABLE 12.1 Increasing Order of Precedence of Six Functional Groups

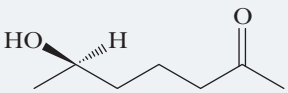
Functional Group	Suffix	Prefix	Example of When the Functional Group Has Lower Priority	
Carboxyl	-oic acid	–		
Aldehyde	-al	oxo-	3-Oxopropanoic acid	
Ketone	-one	oxo-	3-Oxobutanal	
Alcohol	-ol	hydroxy-	4-Hydroxy-2-butanone	
Amino	-amine	amino-	2-Amino-1-propanol	
Sulfhydryl	-thiol	mercapto-	2-Mercaptoethanol	

EXAMPLE 12.3

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

STRATEGY

First determine the root name from the longest chain of carbons that contains the carbonyl group. Use the priority rules in Table 12.1 to determine the suffix and prefix. For benzene ring compounds, remember to use any common names that have been retained in the IUPAC system.

SOLUTION

(a) An aldehyde has higher precedence than a ketone, so we indicate the presence of the carbonyl group of the ketone by the prefix *oxo-*. The IUPAC name of this compound is 5-oxohexanal.

(b) The carboxyl group has higher precedence, so we indicate the presence of the amino group by the prefix *amino-*. The IUPAC name is 4-aminobenzoic acid. Alternatively, the compound may be named *p*-aminobenzoic acid, abbreviated PABA. PABA, a growth factor of microorganisms, is required for the synthesis of folic acid.

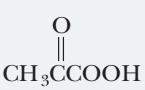
(c) The C═O group has higher precedence than the —OH group, so we indicate the —OH group by the prefix *hydroxy-*. The IUPAC name of this compound is (*R*)-6-hydroxy-2-heptanone.

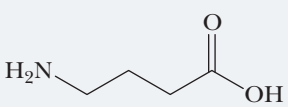
See problems 12.17, 12.18

PROBLEM 12.3

Write IUPAC names for each compound, each of which is important in intermediary metabolism:

(a) 
Lactic acid

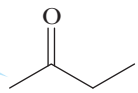
(b) 
Pyruvic acid

(c) 
γ-Aminobutyric acid

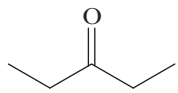
The name shown is the one by which the compound is more commonly known in the biological sciences.

Common names for ketones are derived by naming each alkyl or aryl group bonded to the carbonyl group as a separate word, followed by the word *ketone*. Groups are generally listed in order of increasing atomic weight. Methyl ethyl ketone, abbreviated MEK, is a common solvent for varnishes and lacquers:

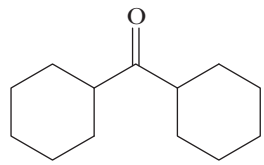
the lower-molecular-weight group bonded to the carbonyl comes first in the common name for a ketone



Methyl ethyl ketone (MEK)



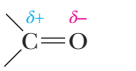
Diethyl ketone



Dicyclohexyl ketone

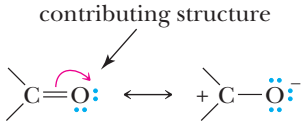
12.3 What Are the Physical Properties of Aldehydes and Ketones?

Oxygen is more electronegative than carbon (3.5 compared with 2.5; Table 1.4); therefore, a carbon–oxygen double bond is polar, with oxygen bearing a partial negative charge and carbon bearing a partial positive charge:

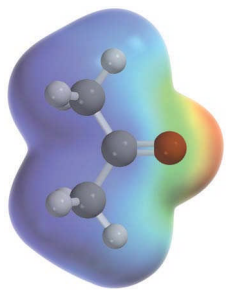


Polarity of a carbonyl group

the more important contributing structure



A carbonyl group as a resonance hybrid



the electron density model shows that the partial positive charge on an acetone molecule is distributed both on the carbonyl carbon and on the two attached methyl groups as well

In addition, the resonance structure on the right emphasizes that, in reactions of a carbonyl group, carbon acts as an electrophile and a Lewis acid. The carbonyl oxygen, by contrast, acts as a nucleophile and a Lewis base.

Because of the polarity of the carbonyl group, aldehydes and ketones are polar compounds and interact in the liquid state by dipole–dipole interactions. As a result, aldehydes and ketones have higher boiling points than those of nonpolar compounds with comparable molecular weight.

Table 12.2 lists the boiling points of six compounds of comparable molecular weight. Pentane and diethyl ether have the lowest boiling points of these six compounds. Both butanal and 2-butanone are polar compounds, and because of the intermolecular attrac-

TABLE 12.2 Boiling Points of Six Compounds of Comparable Molecular Weight

Name	Structural Formula	Molecular Weight	Boiling Point (°C)
Diethyl ether	$CH_3CH_2OCH_2CH_3$	74	34
Pentane	$CH_3CH_2CH_2CH_2CH_3$	72	36
Butanal	$CH_3CH_2CH_2CHO$	72	76
2-Butanone	$CH_3CH_2COCH_3$	72	80
1-Butanol	$CH_3CH_2CH_2CH_2OH$	74	117
Propanoic acid	CH_3CH_2COOH	72	141

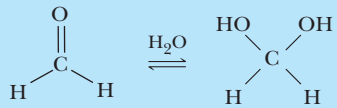
tion between carbonyl groups, their boiling points are higher than those of pentane and diethyl ether. Alcohols (Section 8.1C) and carboxylic acids (Section 13.3) are polar compounds, and their molecules associate by hydrogen bonding; their boiling points are higher than those of butanal and 2-butanone, compounds whose molecules cannot associate in that manner.

Because the carbonyl groups of aldehydes and ketones interact with water molecules by hydrogen bonding, low-molecular-weight aldehydes and ketones are more soluble in water than are nonpolar compounds of comparable molecular weight. Table 12.3 lists the boiling points and solubilities in water of several low-molecular-weight aldehydes and ketones.

TABLE 12.3 Physical Properties of Selected Aldehydes and Ketones

IUPAC Name	Common Name	Structural Formula	Boiling Point (°C)	Solubility (g/100 g water)
Methanal	Formaldehyde	HCHO	−21	infinite
Ethanal	Acetaldehyde	CH_3CHO	20	infinite
Propanal	Propionaldehyde	CH_3CH_2CHO	49	16
Butanal	Butyraldehyde	$CH_3CH_2CH_2CHO$	76	7
Hexanal	Caproaldehyde	$CH_3(CH_2)_4CHO$	129	slight
Propanone	Acetone	CH_3COCH_3	56	infinite
2-Butanone	Methyl ethyl ketone	$CH_3COCH_2CH_3$	80	26
3-Pentanone	Diethyl ketone	$CH_3CH_2COCH_2CH_3$	101	5

although the "solubilities" of methanal and ethanal are reported as "infinite," it should be noted that upon addition to water, 99% of initial methanal and 57% of initial ethanal molecules are converted to compounds known as hydrates

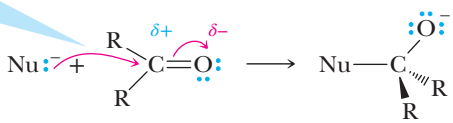


Hydrate of methanal

12.4 What Is the Most Common Reaction Theme of Aldehydes and Ketones?

The partially positive charge on the carbonyl carbon (Section 12.3) is the cause of the most common reaction theme of the carbonyl group, the addition of a nucleophile to form a **tetrahedral carbonyl addition intermediate**. In the following general reaction, the nucleophilic reagent is written as $Nu:^-$ to emphasize the presence of its unshared pair of electrons:

this is the common mechanism pattern: **Reaction of a nucleophile and an electrophile to form a covalent bond**



Tetrahedral carbonyl addition intermediate

12.5 What Are Grignard Reagents, and How Do They React with Aldehydes and Ketones?

From the perspective of the organic chemist, the addition of carbon nucleophiles is the most important type of nucleophilic addition to a carbonyl group because these reactions form new carbon–carbon bonds. In this section, we describe the preparation and reactions of Grignard reagents and their reaction with aldehydes and ketones.

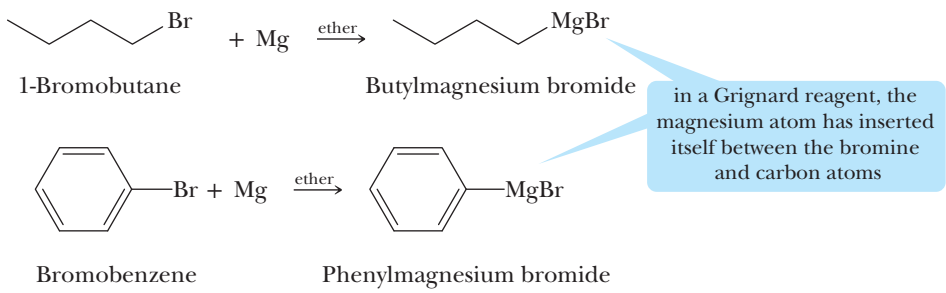
A. Formation and Structure of Organomagnesium Compounds

Alkyl, aryl, and vinylic halides react with Group I, Group II, and certain other metals to form **organometallic compounds**. Within the range of organometallic compounds, organomagnesium compounds are among the most readily available, easily prepared, and easily handled. They are commonly named **Grignard reagents**, after Victor Grignard, who was awarded the 1912 Nobel Prize in Chemistry for their discovery and their application to organic synthesis.

Organometallic compound A compound containing a carbon–metal bond.

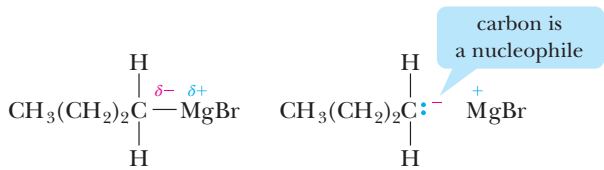
Grignard reagents An organomagnesium compound of the type RMgX or ArMgX.

Grignard reagents are typically prepared by the slow addition of a halide to a stirred suspension of magnesium metal in an ether solvent, most commonly diethyl ether or tetrahydrofuran (THF). Organoiodides and bromides generally react rapidly under these conditions, whereas chlorides react more slowly. Butylmagnesium bromide, for example, is prepared by adding 1-bromobutane to an ether suspension of magnesium metal. Aryl Grignards, such as phenylmagnesium bromide, are prepared in a similar manner:



Given that the difference in electronegativity between carbon and magnesium is 1.3 units (2.5 – 1.2), the carbon–magnesium bond is best described as polar covalent, with carbon bearing a partial negative charge and magnesium bearing a partial positive charge. In the structural formula on the right, the carbon–magnesium bond is shown as ionic to emphasize its nucleophilic character. Note that although we can write a Grignard reagent as a **carbanion**, a more accurate representation shows it as a polar covalent compound:

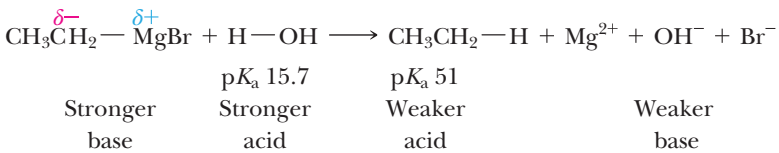
Carbanion An anion in which carbon has an unshared pair of electrons and bears a negative charge.



The feature that makes Grignard reagents so valuable in organic synthesis is that the carbon bearing the halogen is now transformed into a nucleophile.

B. Reaction with Protic Acids

Grignard reagents are very strong bases and react readily with a wide variety of acids (proton donors) to form alkanes. Ethylmagnesium bromide, for example, reacts instantly with water to give ethane and magnesium salts. This reaction is an example of a stronger acid and a stronger base reacting to give a weaker acid and a weaker base (Section 2.4):



Any compound containing an O—H, N—H, and S—H group or a relatively acidic hydrogen will react with a Grignard reagent by proton transfer. Following are examples of compounds containing those functional groups:

HOH	ROH	ArOH	RCOOH	RNH_2	RSH	R—C≡C—H
Water	Alcohols	Phenols	Carboxylic acids	Amines	Thiols	Terminal alkynes

Because Grignard reagents react so rapidly with these proton acids, Grignard reagents cannot be made from any halogen-containing compounds that also contain them.

EXAMPLE 12.4

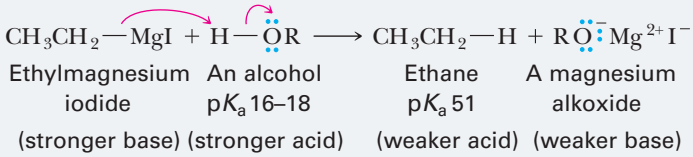
Write an equation for the acid–base reaction between ethylmagnesium iodide and an alcohol. Use curved arrows to show the flow of electrons in this reaction. In addition, show that the reaction is an example of a stronger acid and stronger base reacting to form a weaker acid and weaker base.

STRATEGY

Show the reaction of the Grignard reagent with a generic alcohol (ROH) to form an alkane and a magnesium alkoxide. In drawing the mechanism, remember that the Grignard reagent reacts as a base by donating the electrons in its C—Mg bond to form a new bond to the electrophile (in this case, H^+).

SOLUTION

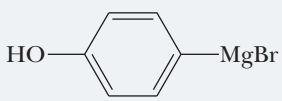
The alcohol is the stronger acid, and ethyl carbanion is the stronger base:

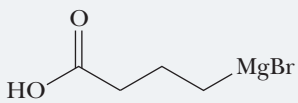


See problems 12.19, 12.21, 12.22

PROBLEM 12.4

Explain how these Grignard reagents react with molecules of their own kind to "self-destruct":

(a) 

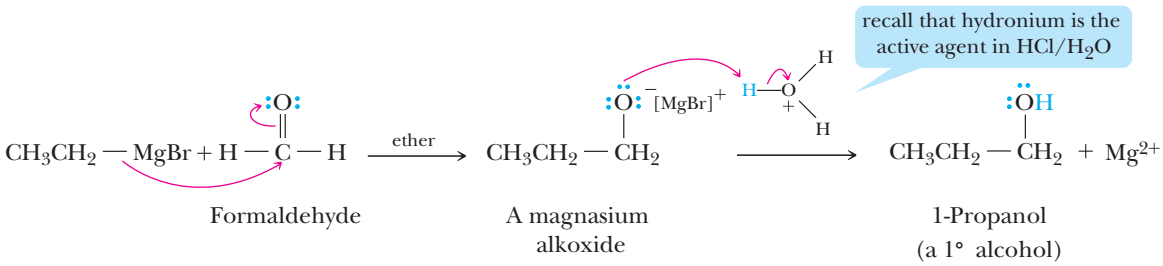
(b) 

C. Addition of Grignard Reagents to Aldehydes and Ketones

The special value of Grignard reagents is that they provide excellent ways to form new carbon–carbon bonds. In their reactions, Grignard reagents behave as carbanions. A carbanion is a good nucleophile and adds to the carbonyl group of an aldehyde or a ketone to form a tetrahedral carbonyl addition intermediate. The driving force for these reactions is the attraction of the partial negative charge on the carbon of the organometallic compound to the partial positive charge of the carbonyl carbon. In the examples that follow, the magnesium–oxygen bond, which forms after the tetrahedral carbonyl addition intermediate is formed, is written $—O^-[MgBr]^+$ to emphasize its ionic character. The alkoxide ions formed in Grignard reactions are strong bases (Section 8.2C) and form alcohols when treated with an aqueous acid such as HCl or aqueous NH_4Cl during workup.

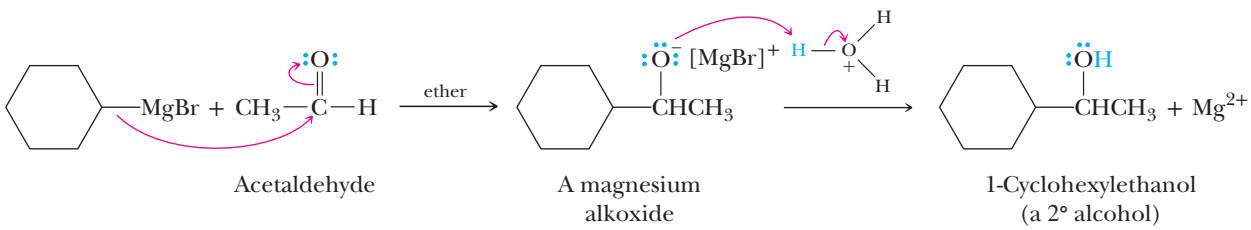
Addition to Formaldehyde Gives a 1° Alcohol

Treatment of a Grignard reagent with formaldehyde, followed by hydrolysis in aqueous acid, gives a primary alcohol:



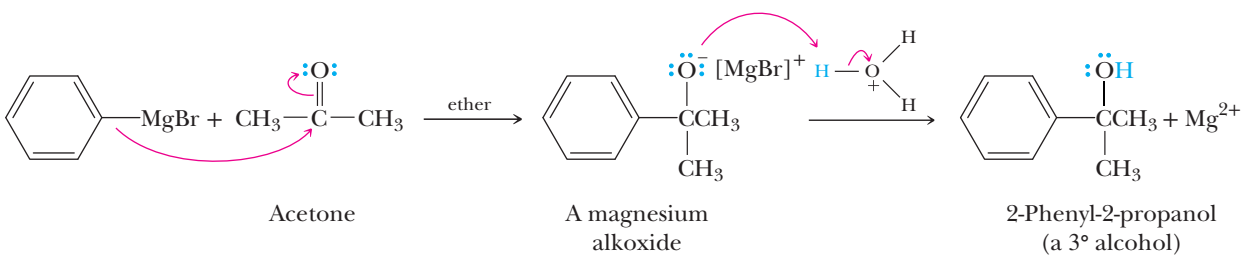
Addition to an Aldehyde (Except Formaldehyde) Gives a 2° Alcohol

Treatment of a Grignard reagent with any aldehyde other than formaldehyde, followed by hydrolysis in aqueous acid, gives a secondary alcohol:



Addition to a Ketone Gives a 3° Alcohol

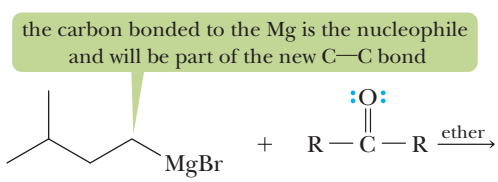
Treatment of a Grignard reagent with a ketone, followed by hydrolysis in aqueous acid, gives a tertiary alcohol:



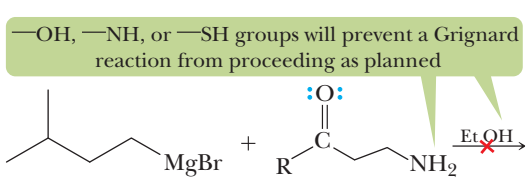
Predict the Product of a Grignard Reaction

HOW TO 12.1

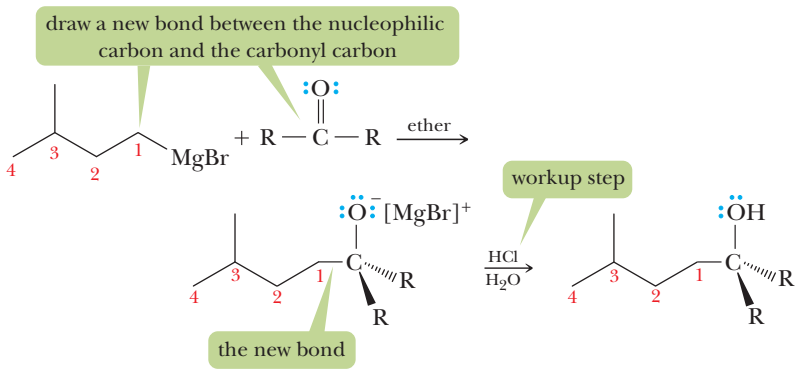
(a) Using the fact that a Grignard reaction involves the formation of a carbon–carbon bond, identify the nucleophilic carbon (i.e., the carbon bonded to the magnesium atom).



(b) Check to see that there are no O—H, N—H, or S—H groups in the reagents or solvent. These will undergo proton transfer with the Grignard reagent and prevent the reaction with the carbonyl from occurring.



(c) Create a new bond between the carbon identified in (a) and the carbonyl carbon. The nucleophilic carbon from the Grignard reagent will no longer be bonded to MgBr. Instead, the MgBr should be shown to be ionically coordinated with the negatively charged oxygen that was part of the carbonyl. If there is a workup step, the magnesium salt is converted to an alcohol.



EXAMPLE 12.5

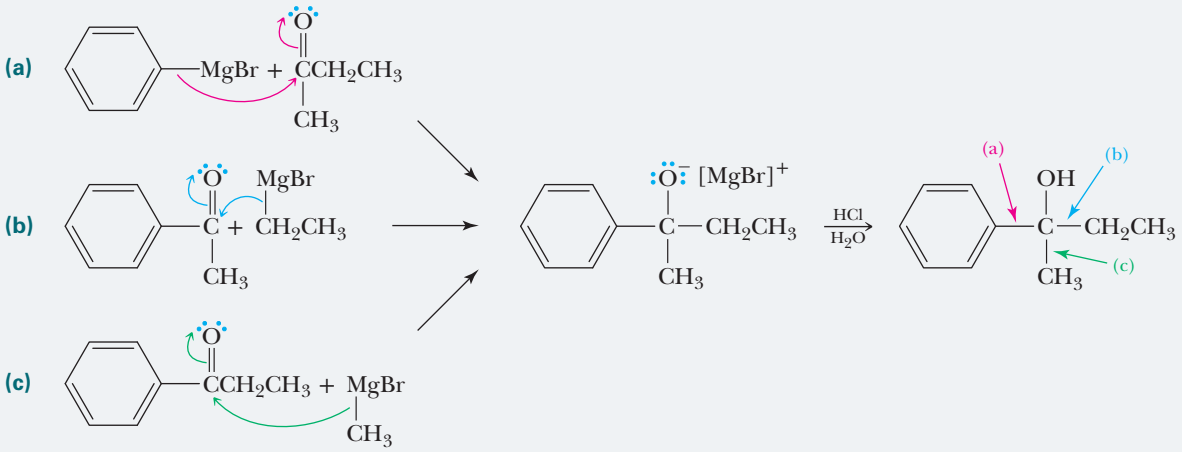
2-Phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.

STRATEGY

The Grignard reagent used to synthesize any alcohol can be determined by identifying a C—C bond connecting the alcohol carbon to the continuing carbon chain. Remove this bond, convert the C—OH to C═O, and convert the other piece to a Grignard reagent.

SOLUTION

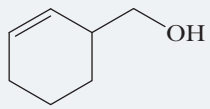
Curved arrows in each solution show the formation of the new carbon–carbon bond and the alkoxide ion, and labels on the final product show which set of reagents forms each bond:

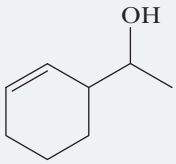


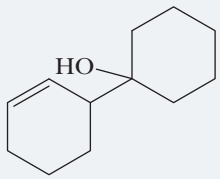
See problems 12.21, 12.22

PROBLEM 12.5

Show how these three compounds can be synthesized from the same Grignard reagent:

(a) 

(b) 

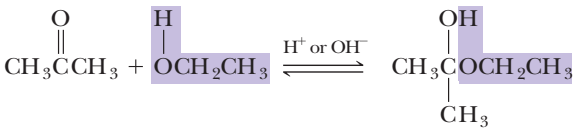
(c) 

12.6 What Are Hemiacetals and Acetals?

A. Formation of Acetals

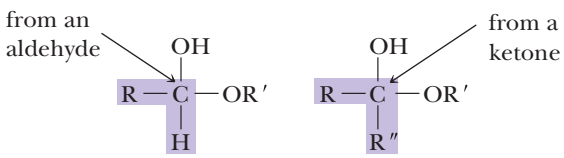
The addition of a molecule of alcohol to the carbonyl group of an aldehyde or a ketone forms a **hemiacetal** (a half-acetal). This reaction is catalyzed by both acid and base: Oxygen adds to the carbonyl carbon and hydrogen adds to the carbonyl oxygen:

Hemiacetal A molecule containing an —OH and an —OR or —OAr group bonded to the same carbon.



A hemiacetal

The functional group of a hemiacetal is a carbon bonded to an —OH group and an —OR or —OAr group:



Hemiacetals

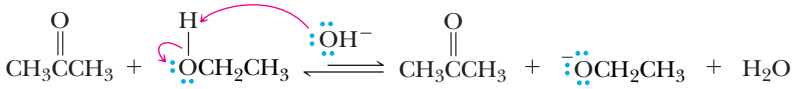
The mechanism for the base-catalyzed conversion of an aldehyde or a ketone to a hemiacetal can be divided into three steps. Note that the base OH^- is a true catalyst in this reaction; it is used in Step 1, but a replacement OH^- is generated in Step 3.

Mechanism

Base-Catalyzed Formation of a Hemiacetal

STEP 1: *Take a proton away.*

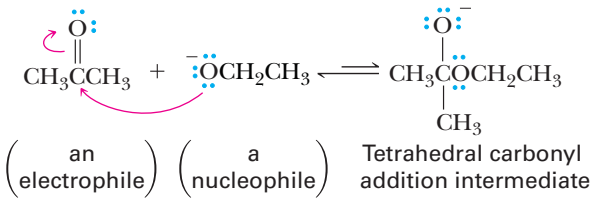
Proton transfer from the alcohol to the base gives an alkoxide ion:



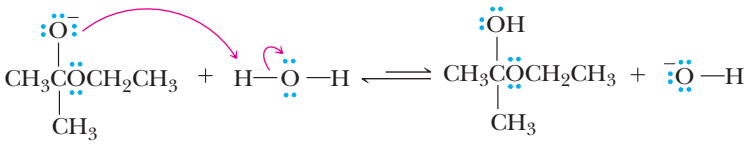
An alkoxide ion

STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*

Addition of the alkoxide ion to the carbonyl gives a tetrahedral carbonyl addition intermediate:



STEP 3: *Add a proton.*
Proton transfer from water to the tetrahedral carbonyl addition intermediate gives the hemiacetal and regenerates the hydroxide ion catalyst:

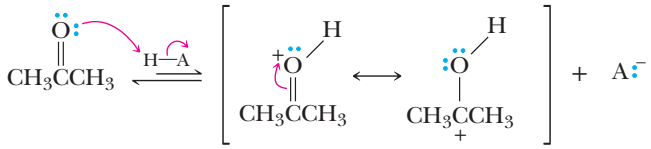


The mechanism for the acid-catalyzed conversion of an aldehyde or ketone to a hemiacetal can be divided into three steps. Note that the acid H—A is a true catalyst in this reaction; it is used in Step 1, but a replacement H—A is generated in Step 3.

Mechanism

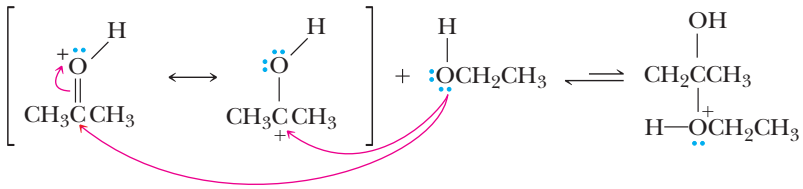
Acid-Catalyzed Formation of a Hemiacetal

STEP 1: *Add a proton.*
Proton transfer from H—A to the carbonyl gives a resonance stabilized cation. The more significant resonance structure places the positive charge on the carbon:



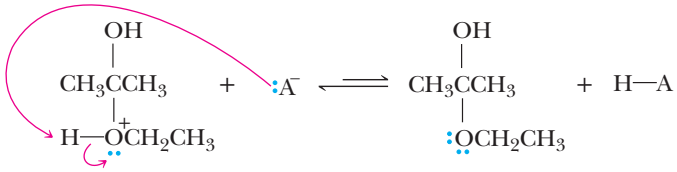
A resonance-stabilized cation

STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*
Addition of the alcohol to the resonance-stabilized cation gives an oxonium ion. *Note*: The attack of the alcohol can be to either contributing structure:

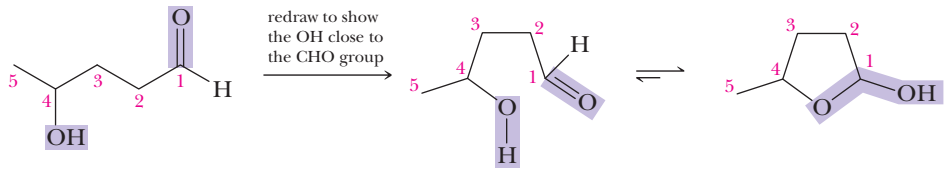


(an electrophile) (a nucleophile) An oxonium ion

STEP 3: *Take a proton away.*
Proton transfer from the oxonium ion to A^- gives the hemiacetal and regenerates the acid catalyst:



Hemiacetals are generally unstable and are only minor components of an equilibrium mixture, except in one very important type of molecule. When a hydroxyl group is part of the same molecule that contains the carbonyl group, and a five- or six-membered ring can form, the compound exists almost entirely in a cyclic hemiacetal form:



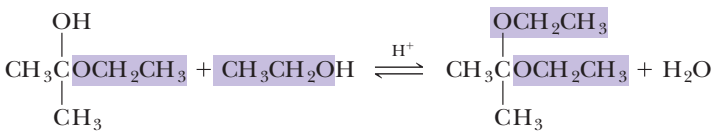
4-Hydroxypentanal

A cyclic hemiacetal (major form present at equilibrium)

We shall have much more to say about cyclic hemiacetals when we consider the chemistry of carbohydrates in Chapter 17.

Hemiacetals can react further with alcohols to form **acetals** plus a molecule of water. This reaction is acid catalyzed:

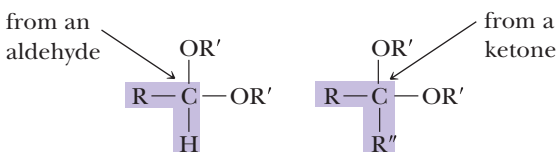
Acetals A molecule containing two —OR or —OAr groups bonded to the same carbon.



A hemiacetal

A diethyl acetal

The functional group of an acetal is a carbon bonded to two —OR or —OAr groups:



Acetals

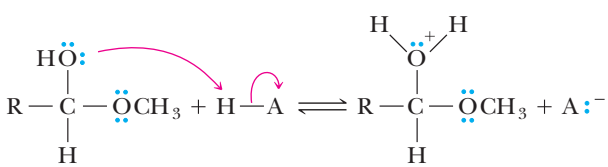
The mechanism for the acid-catalyzed conversion of a hemiacetal to an acetal can be divided into four steps. Note that acid H—A is a true catalyst in this reaction; it is used in Step 1, but a replacement H—A is generated in Step 4.

Mechanism

Acid-Catalyzed Formation of an Acetal

STEP 1: *Add a proton.*

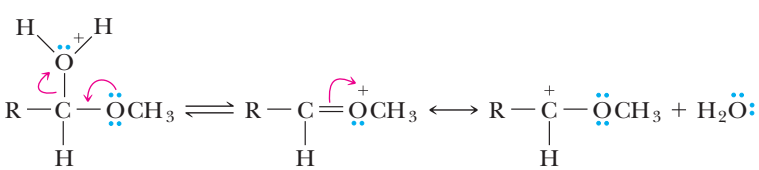
Proton transfer from the acid, H—A, to the hemiacetal OH group gives an oxonium ion:



An oxonium ion

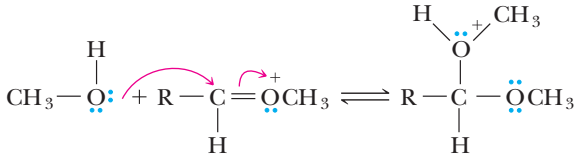
STEP 2: *Break a bond to form a stable ion or molecule.*

Loss of water from the oxonium ion gives a resonance-stabilized cation:



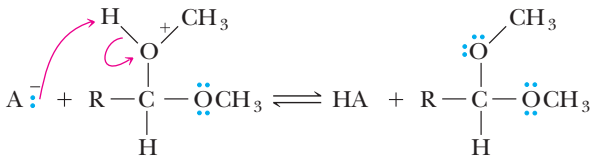
A resonance-stabilized cation

STEP 3: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*
Reaction of the resonance-stabilized cation (an electrophile) with methanol (a nucleophile) gives the conjugate acid of the acetal:



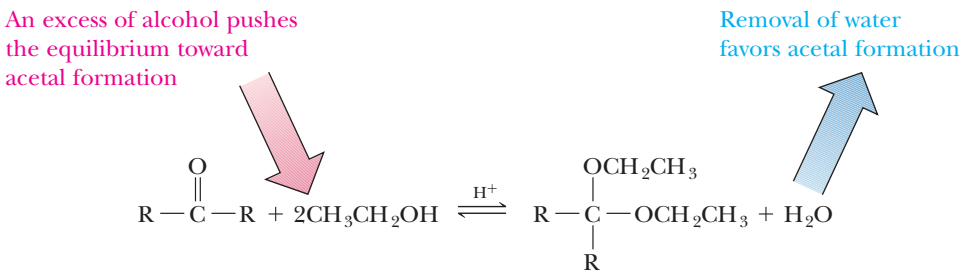
(a nucleophile) (an electrophile) A protonated acetal

STEP 4: *Take a proton away.*
Proton transfer from the protonated acetal to A^- gives the acetal and generates a new molecule of H—A, the acid catalyst:



A protonated acetal An acetal

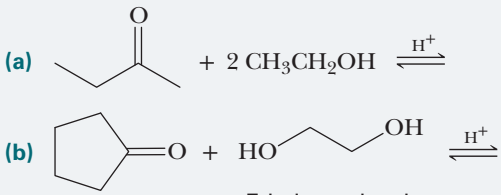
Formation of acetals is often carried out using the alcohol as a solvent and dissolving either dry HCl (hydrogen chloride) or an arenesulfonic acid (Section 9.6B), $ArSO_3H$, in the alcohol. Because the alcohol is both a reactant and the solvent, it is present in large molar excess, which drives the reaction to the right and favors acetal formation. Alternatively, the reaction may be driven to the right by the removal of water as it is formed:



A diethyl acetal

EXAMPLE 12.6

Show the reaction of the carbonyl group of each ketone with one molecule of alcohol to form a hemiacetal and then with a second molecule of alcohol to form an acetal (note that, in part (b), ethylene glycol is a diol, and one molecule of it provides both —OH groups):



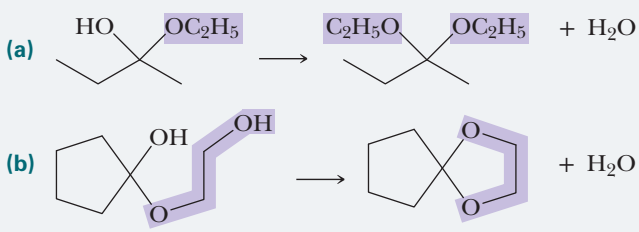
Ethylene glycol

STRATEGY

In forming the hemiacetal, one molecule of the alcohol is added to the carbonyl carbon, resulting in an OR group and an OH group bonded to the carbon that was previously part of the carbonyl. In forming an acetal, two molecules of the alcohol are added to the carbonyl carbon, resulting in two OR groups bonded to the carbon that was previously part of the carbonyl.

SOLUTION

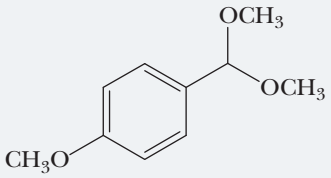
Here are structural formulas of the hemiacetal and then the acetal:

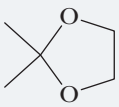


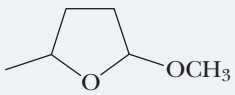
See problems 12.23–12.26

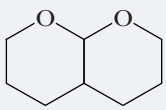
PROBLEM 12.6

The hydrolysis of an acetal forms an aldehyde or a ketone and two alcohols. Following are structural formulas for four acetals:

(a) 

(b) 

(c) 

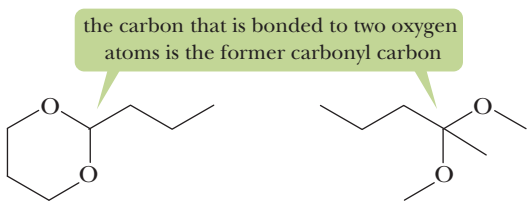
(d) 

Draw the structural formulas for the products of the hydrolysis of each in aqueous acid (i.e., provide the carbonyl compound and alcohol(s) from which each acetal was derived).

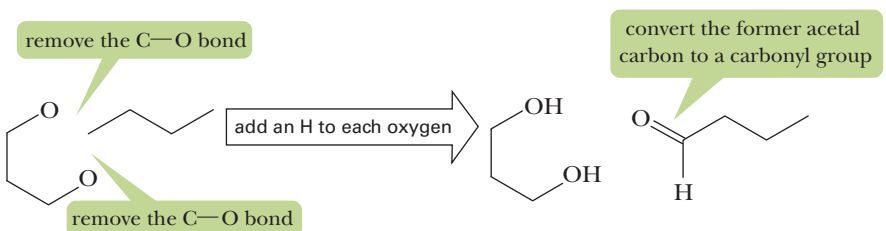
HOW TO 12.2

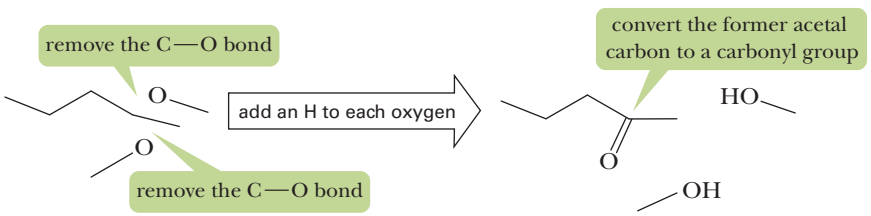
Determine the Reactants Used to Synthesize a Hemiacetal or Acetal

(a) Identify the carbon atom that is bonded to two oxygen atoms. This carbon atom is the carbonyl carbon that was converted to the carbon of the acetal or hemiacetal group.



(b) Remove both C—O bonds and add back a hydrogen to each oxygen to obtain the alcohol reagent(s) used. Then convert the carbon identified in (a) to a carbonyl group.



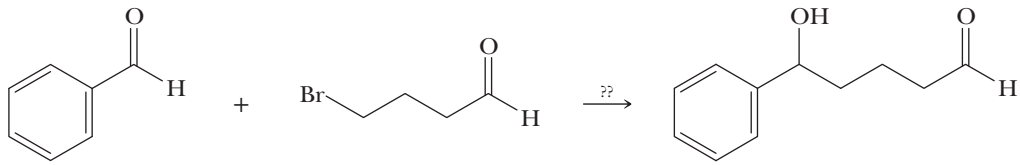


Like ethers, acetals are unreactive to bases, to reducing agents such as H_2/M, to Grignard reagents, and to oxidizing agents (except, of course, those which involve aqueous acid). Because of their lack of reactivity toward these reagents, acetals are often used to

protect the carbonyl groups of aldehydes and ketones while reactions are carried out on functional groups in other parts of the molecule.

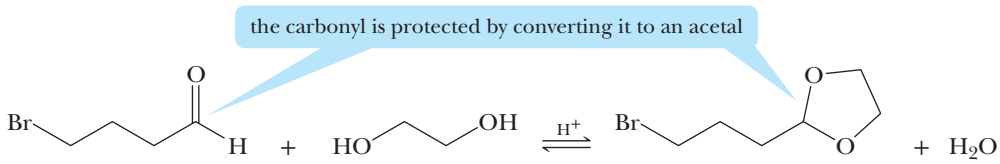
B. Acetals as Carbonyl-Protecting Groups

The use of acetals as carbonyl-protecting groups is illustrated by the synthesis of 5-hydroxy-5-phenylpentanal from benzaldehyde and 4-bromobutanal:



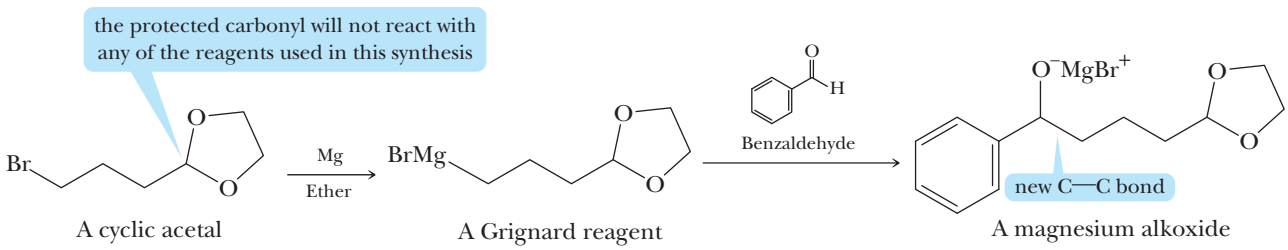
Benzaldehyde 4-Bromobutanal 5-Hydroxy-5-phenylpentanal

One obvious way to form a new carbon–carbon bond between these two molecules is to treat benzaldehyde with the Grignard reagent formed from 4-bromobutanal. This Grignard reagent, however, would react immediately with the carbonyl group of another molecule of 4-bromobutanal, causing it to self-destruct during preparation (Section 12.5B). A way to avoid this problem is to protect the carbonyl group of 4-bromobutanal by converting it to an acetal. Cyclic acetals are often used because they are particularly easy to prepare.



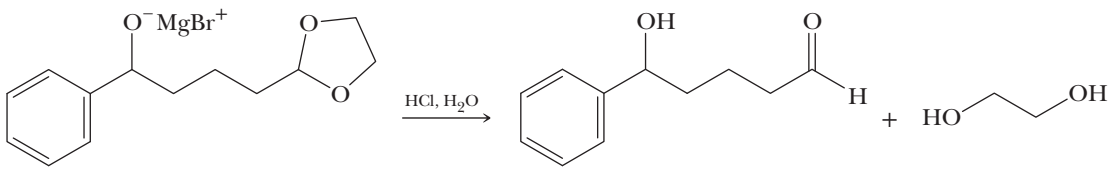
Ethylene glycol A cyclic acetal

Treatment of the protected bromoaldehyde with magnesium in diethyl ether, followed by the addition of benzaldehyde, gives a magnesium alkoxide:



A cyclic acetal A Grignard reagent A magnesium alkoxide

Treatment of the magnesium alkoxide with aqueous acid accomplishes two things. First, protonation of the alkoxide anion gives the desired hydroxyl group, and then, **hydrolysis** of the cyclic acetal regenerates the aldehyde group:



EXAMPLE 12.7

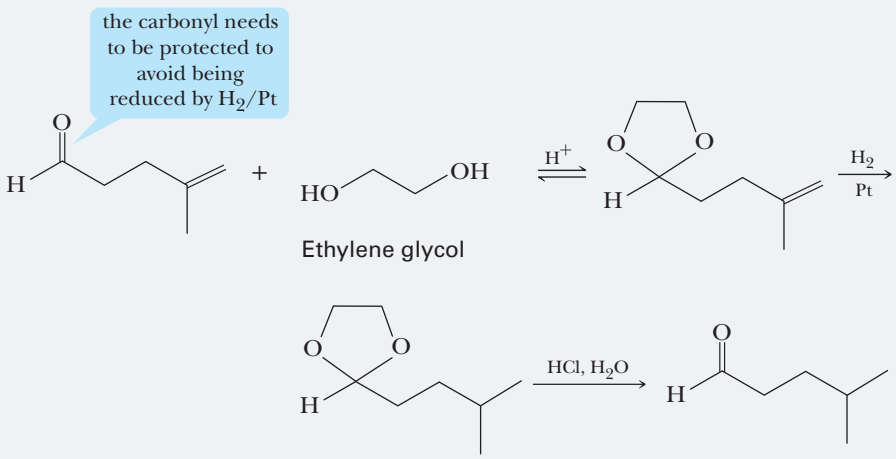
Propose a method for the following transformation. *Note*: Catalytic hydrogenation adds H_2 across C—O double bonds as well as across C—C double bonds.

STRATEGY

Decide which reaction(s) are needed to achieve the interconversion of functional groups. Before applying any reaction to the targeted functional group, determine whether any other functional groups in the compound will react with the reagents proposed. If these other reactions are undesirable, determine whether the functional groups can be protected.

SOLUTION

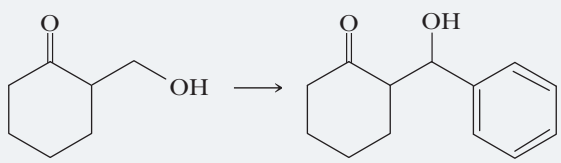
It is important to protect the carbonyl group. Otherwise, it will be reduced to an alcohol by H_2/Pt:



See problems 12.38–12.45

PROBLEM 12.7

Propose a method for the following transformation:



12.7 How Do Aldehydes and Ketones React with Ammonia and Amines?

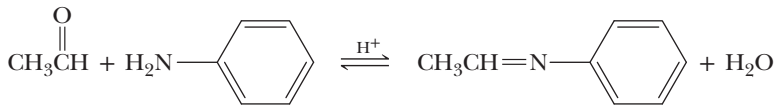
A. Formation of Imines

Ammonia, primary aliphatic amines (RNH_2), and primary aromatic amines ($ArNH_2$) react with the carbonyl group of aldehydes and ketones in the presence of an acid catalyst to give a product that contains a carbon–nitrogen double bond. A molecule

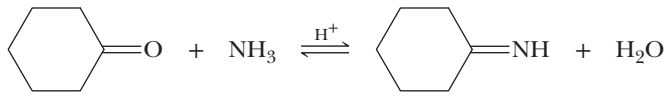
containing a carbon–nitrogen double bond is called an **imine** or, alternatively, a **Schiff base**:

Imine A compound containing a carbon–nitrogen double bond; also called a Schiff base.

Schiff base An alternative name for an imine.

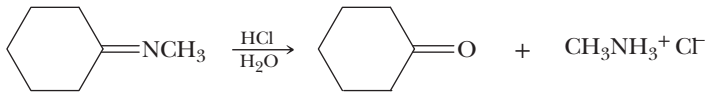


Ethanal Aniline An imine (A Schiff base)



Cyclohexanone Ammonia An imine (A Schiff base)

As with hemiacetal- and acetal-forming reactions, imine formation is reversible; acid-catalyzed hydrolysis of an imine gives a 1° amine and an aldehyde or a ketone. When one (or more) equivalent of acid is used, the 1° amine, a weak base, is converted to an ammonium salt.



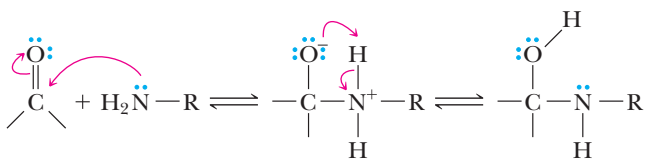
An imine (A Schiff base) Cyclohexanone Ammonium salt

Mechanism

Formation of an Imine from an Aldehyde or a Ketone

STEP 1: *Reaction of an electrophile with a nucleophile to form a new bond.*

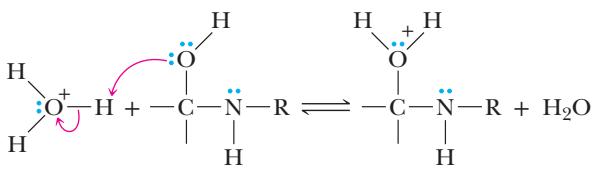
Addition of the nitrogen atom of ammonia or a primary amine, both good nucleophiles, to the carbonyl carbon, followed by a proton transfer, gives a tetrahedral carbonyl addition intermediate:



A tetrahedral carbonyl addition intermediate

STEP 2: *Add a proton.*

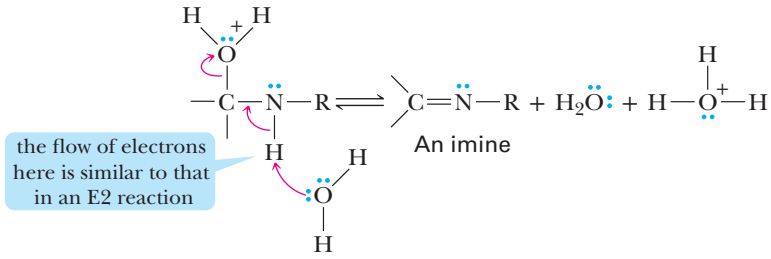
Protonation of the OH group to form $—OH_2^+$, a good leaving group.



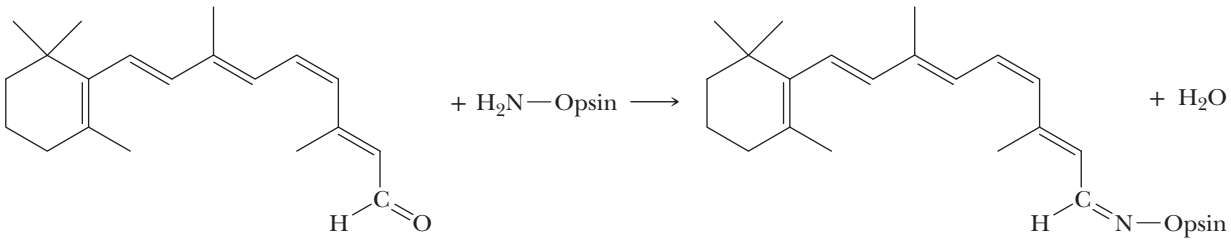
STEP 3: *Take a proton away and break a bond to form a stable molecule.*

Loss of water and proton transfer to solvent gives the imine. Notice that the loss of water and the proton transfer have the characteristics of an E2 reaction. Three things happen simultaneously in this dehydration: a base (in this case a water

molecule) removes a proton from N, the carbon–nitrogen double bond forms, and the leaving group (in this case, a water molecule) departs:

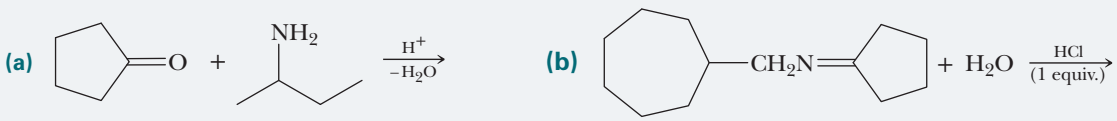


To give but one example of the importance of imines in biological systems, the active form of vitamin A aldehyde (retinal) is bound to the protein opsin in the human retina in the form of an imine called *rhodopsin* or *visual purple* (see Chemical Connections 4B). The amino acid lysine (see Table 18.1) provides the primary amino group for this reaction:



EXAMPLE 12.8

Predict the products formed in each reaction:

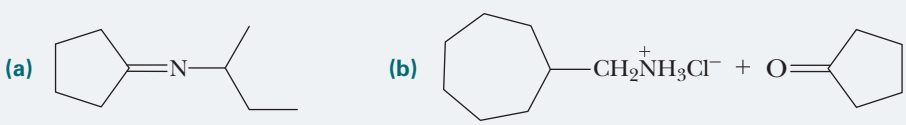


STRATEGY

In an imine-forming reaction, the C═O group is converted to a C═N group and the nitrogen of the former 1° amine loses both of its hydrogens. In the reverse process, the C═N group is converted back to a C═O group and two hydrogens are added back to the nitrogen to form a 1° amine.

SOLUTION

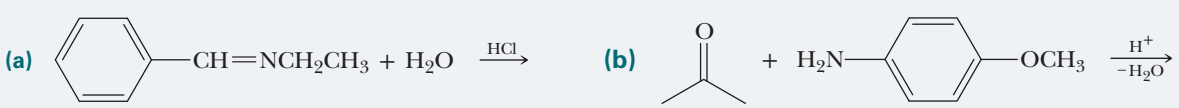
Reaction (a) is an imine-forming reaction, while reaction (b) is the acid-catalyzed hydrolysis of an imine to an ammonium salt and a ketone:



See problems 12.29–12.32

PROBLEM 12.8

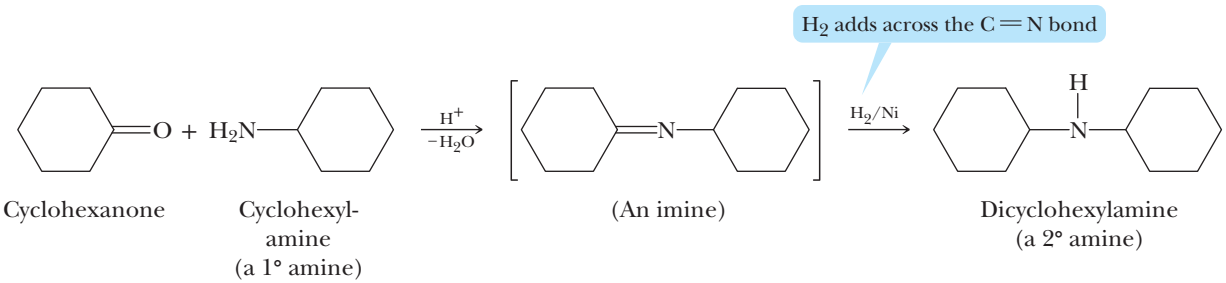
Predict the products formed in each reaction. *Note*: Acid-catalyzed hydrolysis of an imine gives an amine and an aldehyde or a ketone. When one equivalent (or more) of acid is used, the amine is converted to its ammonium salt.



B. Reductive Amination of Aldehydes and Ketones

Reductive amination The formation of an imine from an aldehyde or a ketone, followed by the reduction of the imine to an amine.

One of the chief values of imines is that the carbon–nitrogen double bond can be reduced to a carbon–nitrogen single bond by hydrogen in the presence of a nickel or other transition metal catalyst. By this two-step reaction, called **reductive amination**, a primary amine is converted to a secondary amine by way of an imine, as illustrated by the conversion of cyclohexylamine to dicyclohexylamine:

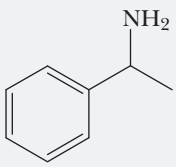


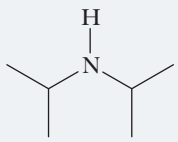
Cyclohexanone — Cyclohexylamine (a 1° amine) — (An imine) — Dicyclohexylamine (a 2° amine)

Conversion of an aldehyde or a ketone to an amine is generally carried out in one laboratory operation by mixing together the carbonyl-containing compound, the amine or ammonia, hydrogen, and the transition metal catalyst. The imine intermediate is not isolated.

EXAMPLE 12.9

Show how to synthesize each amine by a reductive amination:

(a) 

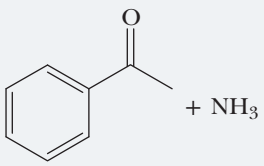
(b) 

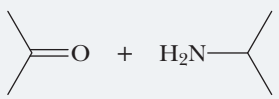
STRATEGY

Identify the C—N bond formed in the reductive amination. The carbon of the C—N bond is part of the carbonyl starting material, and the nitrogen is part of the 1° amine.

SOLUTION

Treat the appropriate compound, in each case a ketone, with ammonia or an amine in the presence of H_2/Ni:

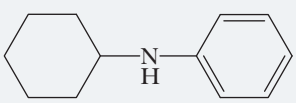
(a) 

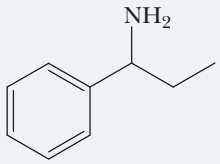
(b) 

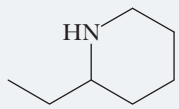
See problems 12.29–12.32

PROBLEM 12.9

Show how to prepare each amine by the reductive amination of an appropriate aldehyde or ketone:

(a) 

(b) 

(c) 

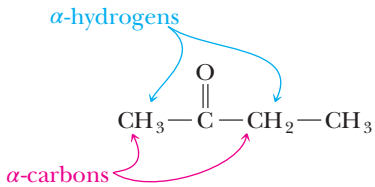
12.8 What Is Keto–Enol Tautomerism?

A. Keto and Enol Forms

A carbon atom adjacent to a carbonyl group is called an **α-carbon**, and any hydrogen atoms bonded to it are called **α-hydrogens**:

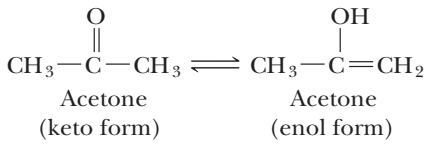
α-Carbon A carbon atom adjacent to a carbonyl group.

α-Hydrogen A hydrogen on an α-carbon.



An aldehyde or ketone that has at least one α-hydrogen is in equilibrium with a constitutional isomer called an **enol**. The name *enol* is derived from the IUPAC designation of it as both an alkene (*-en-*) and an alcohol (*-ol*):

Enol A molecule containing an —OH group bonded to a carbon of a carbon–carbon double bond.



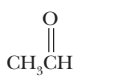
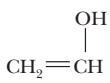
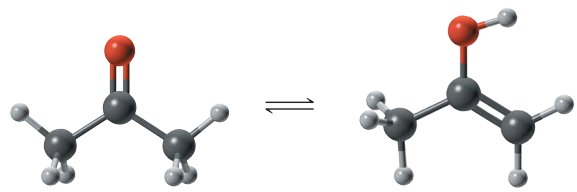
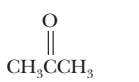
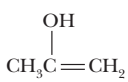
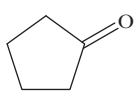
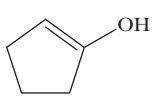
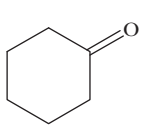
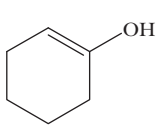
Keto and enol forms are examples of **tautomers**—constitutional isomers that are in equilibrium with each other and that differ in the location of a hydrogen atom and a double bond relative to a heteroatom, most commonly O, S, or N. This type of isomerism is called **tautomerism**.

Tautomers Constitutional isomers that differ in the location of hydrogen and a double bond relative to O, N, or S.

For most simple aldehydes and ketones, the position of the equilibrium in keto–enol tautomerism lies far on the side of the keto form (Table 12.4), because a carbon–oxygen double bond is stronger than a carbon–carbon double bond.

The equilibration of keto and enol forms is catalyzed by acid, as shown in the following two-step mechanism (note that a molecule of H—A is consumed in Step 1, but another is generated in Step 2):

TABLE 12.4 The Position of Keto–Enol Equilibrium for Four Aldehydes and Ketones*

Keto Form		Enol Form	% Enol at Equilibrium	
	⇌		6×10^{-5}	
	⇌		6×10^{-7}	
	⇌		1×10^{-6}	
	⇌		4×10^{-5}	

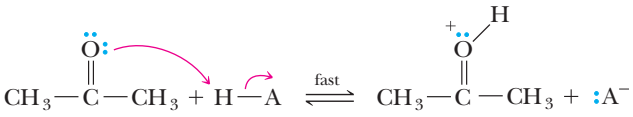
*Data from J. March, *Advanced Organic Chemistry*, 4th ed. (New York, Wiley Interscience, 1992) p. 70.

Mechanism

Acid-Catalyzed Equilibration of Keto and Enol Tautomers

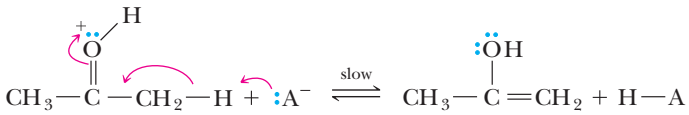
STEP 1: *Add a proton.*

Proton transfer from the acid catalyst, H—A, to the carbonyl oxygen forms the conjugate acid of the aldehyde or ketone:



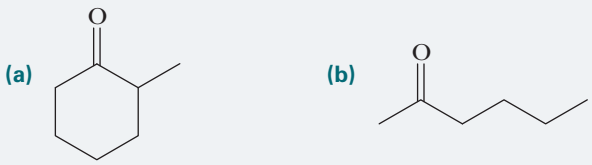
STEP 2: *Take a proton away.*

Proton transfer from the α-carbon to the base, A^-, gives the enol and generates a new molecule of the acid catalyst, H—A:



EXAMPLE 12.10

Write two enol forms for each compound, and state which enol of each predominates at equilibrium:

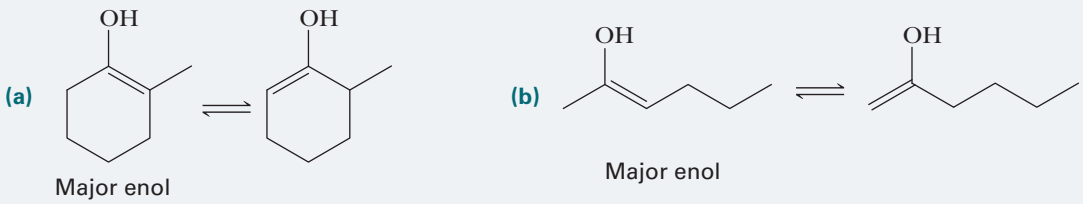


STRATEGY

An enol can form on either side of the carbonyl as long as there is an α-hydrogen to be abstracted in Step 2 of the mechanism. To decide which enol predominates, recall that the more substituted an alkene is, the more stable it is (see Section 5.7).

SOLUTION

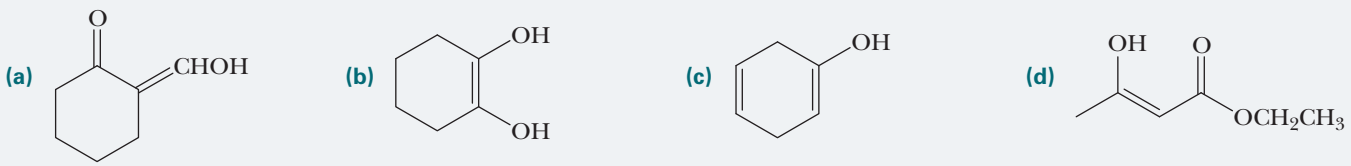
In each case, the major enol form has the more substituted (the more stable) carbon–carbon double bond:



See problem 12.34

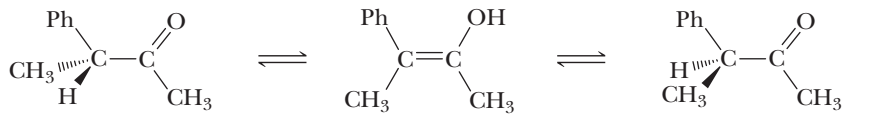
PROBLEM 12.10

Draw the structural formula for the keto form of each enol:



B. Racemization at an α-Carbon

When enantiomerically pure (either *R* or *S*) 3-phenyl-2-butanone is dissolved in ethanol, no change occurs in the optical activity of the solution over time. If, however, a trace of acid (for example, HCl) is added, the optical activity of the solution begins to decrease and gradually drops to zero. When 3-phenyl-2-butanone is isolated from this solution, it is found to be a racemic mixture (Section 6.8C). This observation can be explained by the acid-catalyzed formation of an achiral enol intermediate. Tautomerism of the achiral enol to the chiral keto form generates the *R* and *S* enantiomers with equal probability:



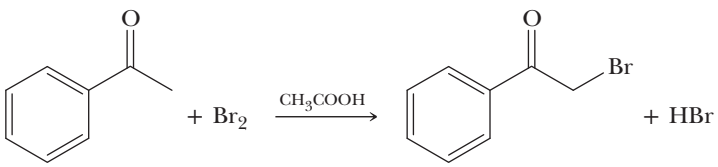
(*R*)-3-Phenyl-2-butanone An achiral enol (*S*)-3-Phenyl-2-butanone

Racemization by this mechanism occurs only at α-carbon stereocenters with at least one α-hydrogen. This process is usually an undesired side effect of acid impurities in a sample, because it is often, in medicine for example, important to have an enantiomerically pure form of a compound rather than a racemic mixture.

Racemization The conversion of a pure enantiomer into a racemic mixture.

C. α-Halogenation

Aldehydes and ketones with at least one α-hydrogen react with bromine and chlorine at the α-carbon to give an α-haloaldehyde or α-haloketone. Acetophenone, for example, reacts with bromine in acetic acid to give an α-bromoketone:



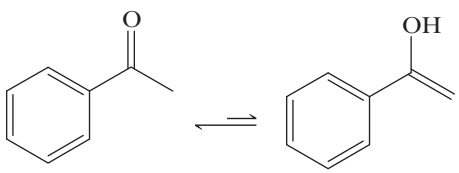
Acetophenone α-Bromoacetophenone

α-Halogenation is catalyzed by both acid and base. For acid-catalyzed halogenation, the HBr or HCl generated by the reaction catalyzes further reaction.

Mechanism

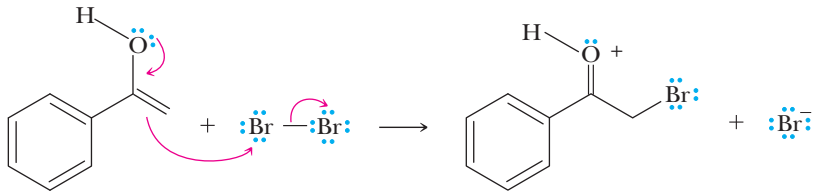
Acid-Catalyzed α-Halogenation of a Ketone

STEP 1: *Keto–enol tautomerism (Section 12.8A).*
A small amount of enol is formed under acid-catalyzed conditions:

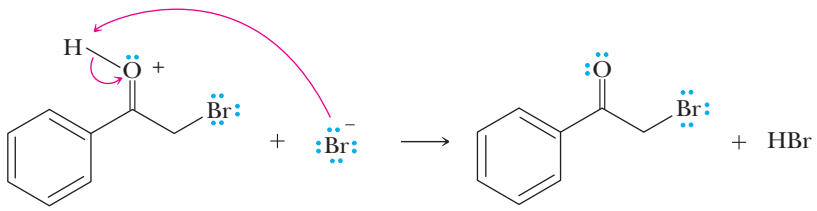


Keto form Enol form

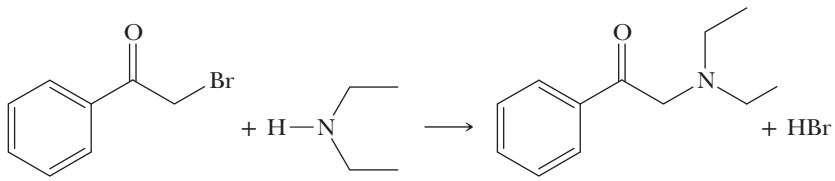
STEP 2: *Reaction of an electrophile with a nucleophile to form a new covalent bond.*
Nucleophilic attack of the enol on the halogen molecule:



STEP 3: *Take a proton away.*
Proton transfer generates HBr and gives the α-haloketone:



The value of α-halogenation is that it converts an α-carbon into a center that now has a good leaving group bonded to it and that is therefore susceptible to attack by a variety of good nucleophiles. In the following illustration, diethylamine (a nucleophile) reacts with the α-bromoketone to give an α-diethylaminoketone:



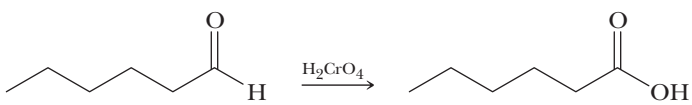
An α-bromoketone — An α-diethylaminoketone

In practice, this type of nucleophilic substitution is generally carried out in the presence of a weak base such as potassium carbonate to neutralize the HX as it is formed.

12.9 How Are Aldehydes and Ketones Oxidized?

A. Oxidation of Aldehydes to Carboxylic Acids

Aldehydes are oxidized to carboxylic acids by a variety of common oxidizing agents, including chromic acid and molecular oxygen. In fact, aldehydes are one of the most easily oxidized of all functional groups. Oxidation by chromic acid (Section 8.2F) is illustrated by the conversion of hexanal to hexanoic acid:



Hexanal — Hexanoic acid

Aldehydes are also oxidized to carboxylic acids by silver ion. One common laboratory procedure uses **Tollens' reagent**, prepared by dissolving $AgNO_3$ in water, adding sodium

hydroxide to precipitate silver ion as Ag_2O, and then adding aqueous ammonia to redissolve silver ion as the silver–ammonia complex ion:

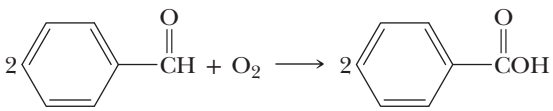
$$Ag^+NO_3^- + 2NH_3 \underset{}{\overset{NH_3,H_2O}{\rightleftharpoons}} Ag(NH_3)_2^+ NO_3^-$$

When Tollens' reagent is added to an aldehyde, the aldehyde is oxidized to a carboxylic anion, and Ag^+ is reduced to metallic silver. If this reaction is carried out properly, silver precipitates as a smooth, mirrorlike deposit—hence the name **silver-mirror test**:

$$RCH + 2Ag(NH_3)_2^+ + H_2O \longrightarrow RCOH + 2Ag + 3NH_4^+ + NH_3$$

Nowadays, Ag^+ is rarely used for the oxidation of aldehydes, because of the cost of silver and because other, more convenient methods exist for this oxidation. The reaction, however, is still used for silvering mirrors. In the process, formaldehyde or glucose is used as the aldehyde to reduce Ag^+.

Aldehydes are also oxidized to carboxylic acids by molecular oxygen and by hydrogen peroxide.



Benzaldehyde Benzoic acid

Molecular oxygen is the least expensive and most readily available of all oxidizing agents, and, on an industrial scale, air oxidation of organic molecules, including aldehydes, is common. Air oxidation of aldehydes can also be a problem: Aldehydes that are liquid at room temperature are so sensitive to oxidation by molecular oxygen that they must be protected from contact with air during storage. Often, this is done by sealing the aldehyde in a container under an atmosphere of nitrogen.

Charles D. Winters

A silver mirror has been deposited in the inside of this flask by the reaction of an aldehyde with Tollens' reagent.

EXAMPLE 12.11

Draw a structural formula for the product formed by treating each compound with Tollens' reagent, followed by acidification with aqueous HCl:

(a) Pentanal **(b)** Cyclopentanecarbaldehyde

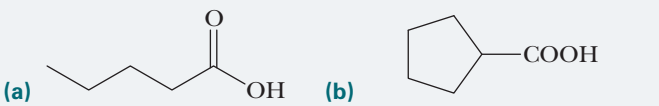
STRATEGY

Aldehydes are oxidized to carboxylic acids by Tollens' reagent.

See problems 12.36, 12.37

SOLUTION

The aldehyde group in each compound is oxidized to a carboxyl group:



(a) Pentanoic acid **(b)** Cyclopentanecarboxylic acid

PROBLEM 12.11

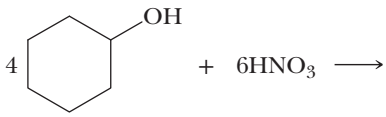
Complete these oxidations:

(a) 3-Oxobutanal + O_2 ⟶ **(b)** 3-Phenylpropanal + Tollens' reagent ⟶

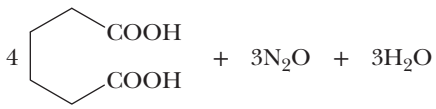
Chemical Connections 12A

A GREEN SYNTHESIS OF ADIPIC ACID

The current industrial production of adipic acid relies on the oxidation of a mixture of cyclohexanol and cyclohexanone by nitric acid:



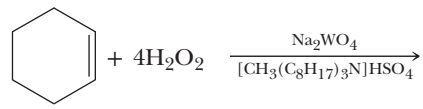
Cyclohexanol



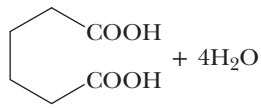
Hexanedioic acid (Adipic acid) Nitrous oxide

A by-product of this oxidation is nitrous oxide, a gas considered to play a role in global warming and the depletion of the ozone layer in the atmosphere, as well as contributing to acid rain and acid smog. Given the fact that worldwide production of adipic acid is approximately 2.2 billion metric tons per year, the production of nitrous oxide is enormous. In spite of technological advances that allow for the recovery and recycling of nitrous oxide, it is estimated that approximately 400,000 metric tons escapes recovery and is released into the atmosphere each year.

Recently, Ryoji Noyori (2001 Nobel Prize in Chemistry) and coworkers at Nagoya University in Japan developed a "green" route to adipic acid, one that involves the oxidation of cyclohexene by 30% hydrogen peroxide catalyzed by sodium tungstate, Na_2WO_4:



Cyclohexene



Hexanedioic acid (Adipic acid)

In this process, cyclohexene is mixed with aqueous 30% hydrogen peroxide, and sodium tungstate and methyltrioctylammonium hydrogen sulfate are added to the resulting two-phase system. (Cyclohexene is insoluble in water.) Under these conditions, cyclohexene is oxidized to adipic acid in approximately 90% yield.

While this route to adipic acid is environmentally friendly, it is not yet competitive with the nitric acid oxidation route because of the high cost of 30% hydrogen peroxide. What will make it competitive is either a considerable reduction in the cost of hydrogen peroxide or the institution of more stringent limitations on the emission of nitrous oxide into the atmosphere (or a combination of these).

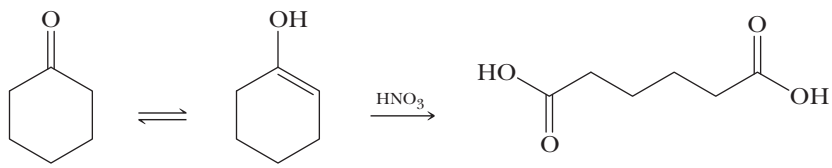
Question

Using chemistry presented in this and previous chapters, propose a synthesis for adipic acid from cyclohexene.

B. Oxidation of Ketones to Carboxylic Acids

Ketones are much more resistant to oxidation than are aldehydes. For example, ketones are not normally oxidized by chromic acid or potassium permanganate. In fact, these reagents are used routinely to oxidize secondary alcohols to ketones in good yield (Section 8.2F).

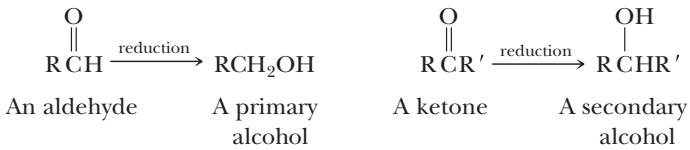
Ketones undergo oxidative cleavage, via their enol form, by potassium dichromate and potassium permanganate at higher temperatures and by higher concentrations of nitric acid, HNO_3. The carbon–carbon double bond of the enol is cleaved to form two carboxyl or ketone groups, depending on the substitution pattern of the original ketone. An important industrial application of this reaction is the oxidation of cyclohexanone to hexanedioic acid (adipic acid), one of the two monomers required for the synthesis of the polymer nylon 66 (Section 16.4A):



Cyclohexanone (keto form) Cyclohexanone (enol form) Hexanedioic acid (Adipic acid)

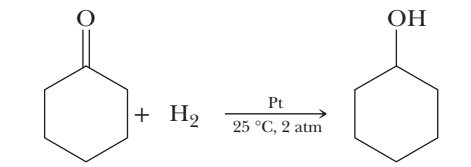
12.10 How Are Aldehydes and Ketones Reduced?

Aldehydes are reduced to primary alcohols and ketones to secondary alcohols:

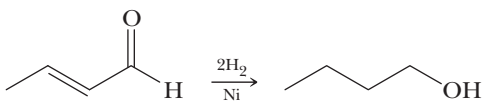


A. Catalytic Reduction

The carbonyl group of an aldehyde or a ketone is reduced to a hydroxyl group by hydrogen in the presence of a transition metal catalyst, most commonly finely divided palladium, platinum, nickel, or rhodium. Reductions are generally carried out at temperatures from 25 to 100 °C and at pressures of hydrogen from 1 to 5 atm. Under such conditions, cyclohexanone is reduced to cyclohexanol:



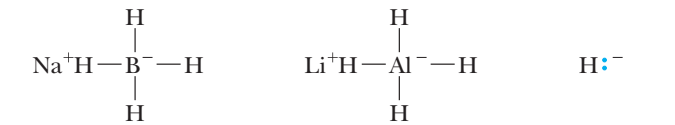
The catalytic reduction of aldehydes and ketones is simple to carry out, yields are generally very high, and isolation of the final product is very easy. A disadvantage is that some other functional groups (for example, carbon–carbon double bonds) are also reduced under these conditions.



B. Metal Hydride Reductions

By far the most common laboratory reagents used to reduce the carbonyl group of an aldehyde or a ketone to a hydroxyl group are sodium borohydride and lithium aluminum hydride. Each of these compounds behaves as a source of **hydride ion**, a very strong nucleophile. The structural formulas drawn here for these reducing agents show formal negative charges on boron and aluminum:

Hydride ion A hydrogen atom with two electrons in its valence shell; H:⁻.



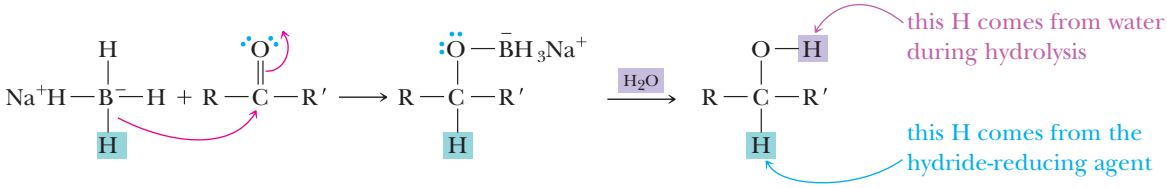
In fact, hydrogen is more electronegative than either boron or aluminum (H = 2.1, Al = 1.5, and B = 2.0), and the formal negative charge in the two reagents resides more on hydrogen than on the metal.

Lithium aluminum hydride is a very powerful reducing agent; it rapidly reduces not only the carbonyl groups of aldehydes and ketones, but also those of carboxylic acids (Section 13.5) and their functional derivatives (Section 14.8). Sodium borohydride is a much more selective reagent, reducing only aldehydes and ketones rapidly.

Reductions using sodium borohydride are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol. The initial product of reduction is a tetraalkyl borate, which is converted to an alcohol and sodium borate salts upon treatment with water. One mole of sodium borohydride reduces 4 moles of aldehyde or ketone:

$$4R\underset{\displaystyle O}{\overset{\displaystyle \|}{C}}H + NaBH_4 \xrightarrow{CH_3OH} \underset{\text{A tetraalkyl borate}}{(RCH_2O)_4B^-Na^+} \xrightarrow{H_2O} 4RCH_2OH + \text{borate salts}$$

The key step in the metal hydride reduction of an aldehyde or a ketone is the transfer of a hydride ion from the reducing agent to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. In the reduction of an aldehyde or a ketone to an alcohol, only the hydrogen atom bonded to carbon comes from the hydride-reducing agent; the hydrogen atom bonded to oxygen comes from the water added to hydrolyze the metal alkoxide salt.



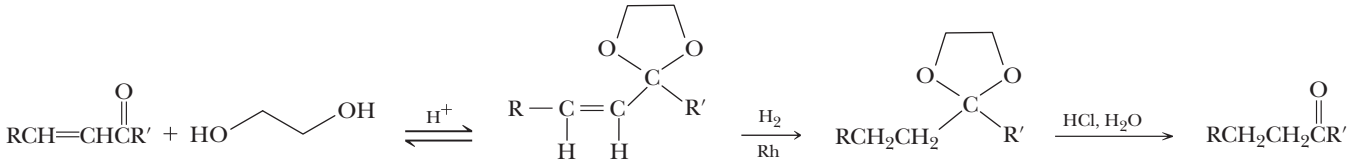
The next two equations illustrate the selective reduction of a carbonyl group in the presence of a carbon–carbon double bond and, alternatively, the selective reduction of a carbon–carbon double bond in the presence of a carbonyl group.

Selective reduction of a carbonyl group:

$$RCH{=}CH\underset{\displaystyle O}{\overset{\displaystyle \|}{C}}R' \xrightarrow[2)\ H_2O]{1)\ NaBH_4} RCH{=}CH\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}HR'$$

A carbon–carbon double bond can be reduced selectively in the presence of a carbonyl group by first protecting the carbonyl group using an acetal.

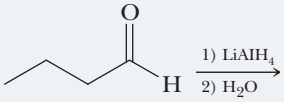
Selective reduction of a carbon–carbon double bond using a protecting group:



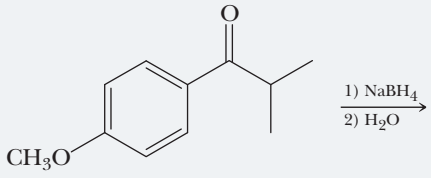
EXAMPLE 12.12

Complete these reductions:

(a)



(b)

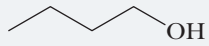


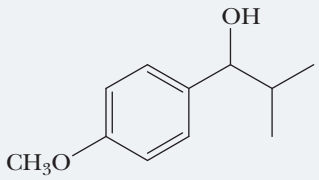
STRATEGY

Consider all the functional groups that can react with each reducing reagent. Alkenes, ketones, aldehydes, and imines are just some examples of functional groups that can be reduced.

SOLUTION

The carbonyl group of the aldehyde in (a) is reduced to a primary alcohol, and that of the ketone in (b) is reduced to a secondary alcohol:

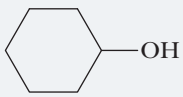
(a) 

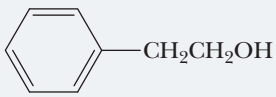
(b) 

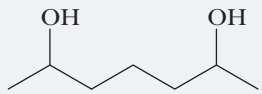
See problems 12.36, 12.37

PROBLEM 12.12

What aldehyde or ketone gives each alcohol upon reduction by $NaBH_4$?

(a) 

(b) 

(c) 

SUMMARY OF KEY QUESTIONS

12.1 What Are Aldehydes and Ketones?

- An **aldehyde** contains a carbonyl group bonded to a hydrogen atom and a carbon atom.
- A **ketone** contains a carbonyl group bonded to two carbons.

12.2 How Are Aldehydes and Ketones Named?

- An aldehyde is named by changing *-e* of the parent alkane to *-al*.
- A CHO group bonded to a ring is indicated by the suffix *-carbaldehyde*.
- A ketone is named by changing *-e* of the parent alkane to *-one* and using a number to locate the carbonyl group.
- In naming compounds that contain more than one functional group, the IUPAC system has established an **order of precedence of functional groups**. If the carbonyl group of an aldehyde or a ketone is lower in precedence than other functional groups in the molecule, it is indicated by the infix **-oxo-**.

12.3 What Are the Physical Properties of Aldehydes and Ketones?

- Aldehydes and ketones are polar compounds and interact in the pure state by dipole–dipole interactions.
- Aldehydes and ketones have higher boiling points and are more soluble in water than are nonpolar compounds of comparable molecular weight.

12.4 What Is the Most Common Reaction Theme of Aldehdyes and Ketones?

- The common reaction theme of the carbonyl group of aldehydes and ketones is the addition of a nucleophile to form a **tetrahedral carbonyl addition intermediate**.

12.5 What Are Grignard Reagents, and How Do They React with Aldehydes and Ketones?

- **Grignard reagents** are organomagnesium compounds with the generic formula RMgX or ArMgX.
- The carbon–metal bond in Grignard reagents has a high degree of partial ionic character.
- Grignard reagents behave as **carbanions** and are both strong bases and good nucleophiles. They react with aldehydes and ketones by adding to the carbonyl carbon.

12.6 What Are Hemiacetals and Acetals?

- The addition of a molecule of alcohol to the carbonyl group of an aldehyde or a ketone forms a **hemiacetal**.
- Hemiacetals can react further with alcohols to form **acetals** plus a molecule of water.
- Because of their lack of reactivity toward nucleophilic and basic reagents, acetals are often used to protect the carbonyl groups of aldehydes and ketones while reactions are carried out on functional groups in other parts of the molecule.

12.7 How Do Aldehydes and Ketones React with Ammonia and Amines?

- Ammonia, 1° aliphatic amines (RNH_2), and 1° aromatic amines ($ArNH_2$) react with the carbonyl group of aldehydes and ketones in the presence of an acid catalyst to give **imines**, compounds that contain a carbon–nitrogen double bond.

12.8 What Is Keto–Enol Tautomerism?

- A carbon atom adjacent to a carbonyl group is called an **α-carbon**, and any hydrogen atoms bonded to it are called **α-hydrogens**.
- An aldehyde or a ketone, which is said to be in its **keto** form, that has at least one α-hydrogen is in equilibrium with a constitutional isomer called an **enol**. This type of isomerism is called **tautomerism**.
- Tautomerism, catalyzed by trace amounts of acid or base, is the cause of **racemization** of chiral aldehydes and ketones when a stereocenter exists at an α-carbon.
- The enol form allows aldehydes and ketones to be halogenated at the α-position.

12.9 How Are Aldehydes and Ketones Oxidized?

- Aldehydes are oxidized to carboxylic acids by a variety of common oxidizing agents, including chromic acid, the Tollens' reagent, and molecular oxygen.
- Ketones are much more resistant to oxidation than are aldehydes. However, they undergo **oxidative cleavage**, via their enol form, by potassium dichromate and potassium permanganate at higher temperatures and by higher concentrations of HNO_3.

12.10 How Are Aldehydes and Ketones Reduced?

- Aldehydes are reduced to primary alcohols and ketones to secondary alcohols by catalytic hydrogenation or through the use of the metal hydrides $NaBH_4$ or $LiAlH_4$.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. In a compound that contains both an aldehyde and a C—C double bond, each functional group can be reduced exclusive of the other. (12.10)
2. Nucleophiles react with aldehydes and ketones to form tetrahedral carbonyl addition intermediates. (12.4)
3. The carboxyl group (COOH) has a higher priority in naming than all other functional groups. (12.2)
4. A stereocenter at the α-carbon of an aldehyde or a ketone will undergo racemization over time in the presence of an acid or a base. (12.8)
5. Acetone is the lowest-molecular-weight ketone. (12.3)
6. Aldehydes can be oxidized to ketones and carboxylic acids. (12.9)
7. Ketones are less water soluble than alcohols with comparable molecular weight. (12.3)
8. A Grignard reagent cannot be formed in the presence of an NH, OH, or SH group. (12.5)
9. Ketones have higher boiling points than alkanes with comparable molecular weight. (12.3)
10. An aldehyde has a higher priority in naming than a ketone. (12.2)
11. A Grignard reagent is a good electrophile. (12.5)
12. Any reaction that oxidizes an aldehyde to a carboxylic acid will also oxidize a ketone to a carboxylic acid. (12.9)
13. Aldehydes are more water soluble than ethers with comparable molecular weight. (12.3)
14. Aldehydes react with Grignard reagents (followed by acid workup) to form 1° alcohols. (12.5)
15. An imine can be reduced to an amine through catalytic hydrogenation. (12.7)
16. Sodium borohydride, $NaBH_4$, is more reactive and less selective than lithium aluminum hydride, $LiAlH_4$. (12.10)
17. An acetal can only result from the base-catalyzed addition of an alcohol to a hemiacetal. (12.6)
18. A Grignard reagent is a strong base. (12.5)
19. Acetal formation is reversible. (12.6)
20. An imine is the result of the reaction of a 2° amine with an aldehyde or a ketone. (12.7)
21. Ketones react with Grignard reagents (followed by acid workup) to form 2° alcohols. (12.5)
22. Aldehydes and ketones can undergo tautomerism. (12.8)
23. Acetaldehyde is the lowest-molecular-weight aldehyde. (12.3)
24. A ketone that possesses an α-hydrogen can undergo α-halogenation. (12.8)
25. A carbonyl group is polarized such that the oxygen atom is partially positive and the carbon atom is partially negative. (12.3)

26. Acetals are stable to bases, nucleophiles, and reducing agents. (12.6)

27. A "carbaldehyde" is an aldehyde in which the carbonyl group is adjacent to a C—C double bond. (12.1)

28. A hemiacetal can result from the acid-catalyzed or base-catalyzed addition of an alcohol to an aldehyde or a ketone. (12.6)

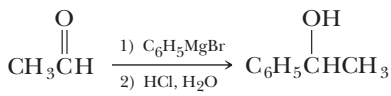
Answers: (1) T (2) T (3) T (4) T (5) T (6) T (7) T (8) T (9) T (10) T
(11) F (12) F (13) T (14) F (15) T (16) F (17) F (18) T (19) T (20) F
(21) F (22) T (23) F (24) T (25) F (26) T (27) F (28) T

Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

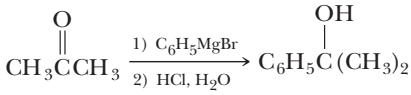
KEY REACTIONS

1. Reaction with Grignard Reagents (Section 12.5C)

Treatment of formaldehyde with a Grignard reagent, followed by hydrolysis in aqueous acid, gives a primary alcohol. Similar treatment of any other aldehyde gives a secondary alcohol:

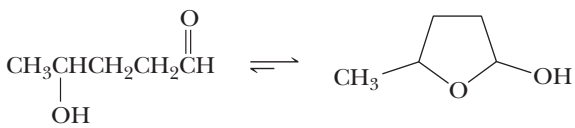


Treatment of a ketone with a Grignard reagent gives a tertiary alcohol:



2. Addition of Alcohols to Form Hemiacetals (Section 12.6)

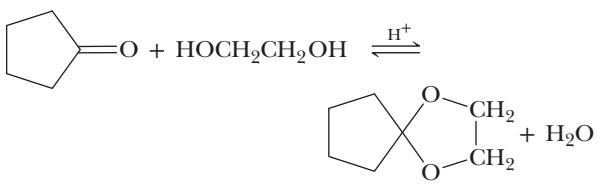
Hemiacetals are only minor components of an equilibrium mixture of aldehyde or ketone and alcohol, except where the —OH and C═O groups are parts of the same molecule and a five- or six-membered ring can form:



4-Hydroxypentanal — A cyclic hemiacetal

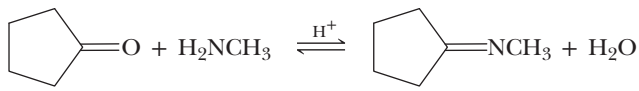
3. Addition of Alcohols to Form Acetals (Section 12.6)

The formation of acetals is catalyzed by acid:



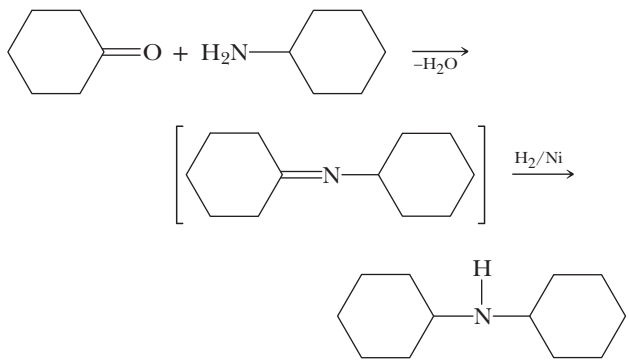
4. Addition of Ammonia and Amines (Section 12.7)

The addition of ammonia or a primary amine to the carbonyl group of an aldehyde or a ketone forms a tetrahedral carbonyl addition intermediate. Loss of water from this intermediate gives an imine (a Schiff base):



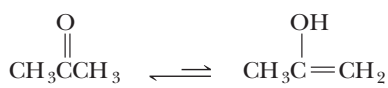
5. Reductive Amination to Amines (Section 12.7B)

The carbon–nitrogen double bond of an imine can be reduced by hydrogen in the presence of a transition metal catalyst to a carbon–nitrogen single bond:



6. Keto–Enol Tautomerism (Section 12.8A)

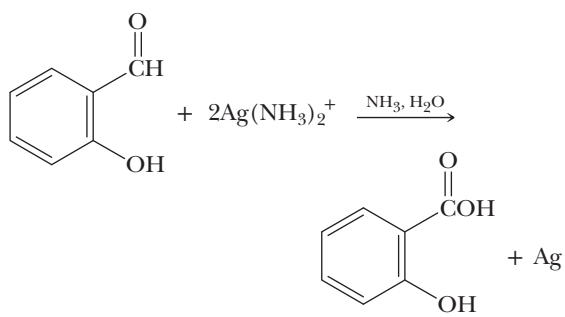
The keto form generally predominates at equilibrium:



Keto form (Approx 99.9%) — Enol form

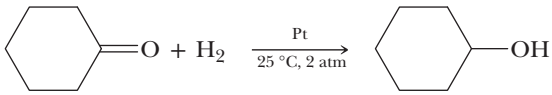
7. Oxidation of an Aldehyde to a Carboxylic Acid (Section 12.9)

The aldehyde group is among the most easily oxidized functional groups. Oxidizing agents include H_2CrO_4, Tollens' reagent, and O_2:



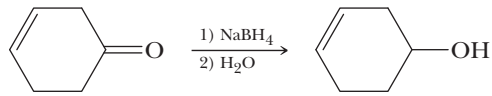
8. Catalytic Reduction (Section 12.10A)

Catalytic reduction of the carbonyl group of an aldehyde or a ketone to a hydroxyl group is simple to carry out, and yields of alcohols are high:



9. Metal Hydride Reduction (Section 12.10B)

Both $LiAlH_4$ and $NaBH_4$ reduce the carbonyl group of an aldehyde or a ketone to an hydroxyl group. They are selective in that neither reduces isolated carbon–carbon double and triple bonds:

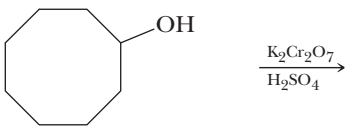


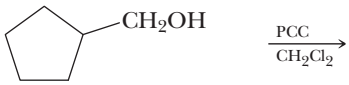
PROBLEMS

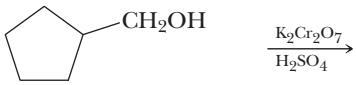
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

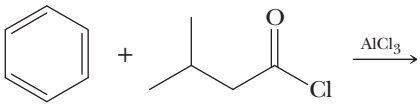
Preparation of Aldehydes and Ketones (see also Chapters 8 and 9)

12.13 Complete these reactions:

(a) 

(b) 

(c) 

(d) 

12.14 Show how you would bring about these conversions:

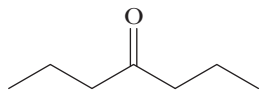
(a) 1-Pentanol to pentanal
(b) 1-Pentanol to pentanoic acid
(c) 2-Pentanol to 2-pentanone
(d) 1-Pentene to 2-pentanone
(e) Benzene to acetophenone
(f) Styrene to acetophenone
(g) Cyclohexanol to cyclohexanone
(h) Cyclohexene to cyclohexanone
(i) Benzene to 2-phenylethanal
(j) 1-Methylcyclohexene to (±)-2-methylcyclohexanone
(k) 1-Hexene to hexanal
(l) 4-bromooctane to 4-octanone
(m) propene to acetone

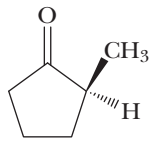
SECTIONS 12.1 AND 12.2 Structure and Nomenclature

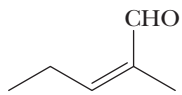
12.15 Draw a structural formula for the one ketone with molecular formula C_4H_8O and for the two aldehydes with molecular formula C_4H_8O. **(See Example 12.2)**

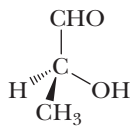
12.16 Draw structural formulas for the four aldehydes with molecular formula $C_5H_{10}O$. Which of these aldehydes are chiral? **(See Example 12.2)**

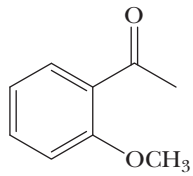
12.17 Name these compounds: **(See Examples 12.1, 12.3)**

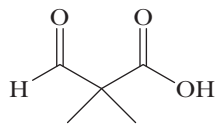
(a) 

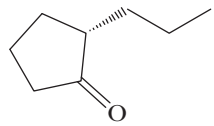
(b) 

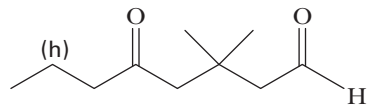
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

12.18 Draw structural formulas for these compounds: **(See Examples 12.1, 12.3)**

(a) 1-Chloro-2-propanone
(b) 3-Hydroxybutanal
(c) 4-Hydroxy-4-methyl-2-pentanone
(d) 3-Methyl-3-phenylbutanal
(e) (*S*)-3-Bromocyclohexanone
(f) 3-Methyl-3-buten-2-one
(g) 5-Oxohexanal
(h) 2,2-Dimethylcyclohexanecarbaldehyde
(i) 3-Oxobutanoic acid
(j) 2-Phenylethanal
(k) (*R*)-2-Methylcyclohexanone
(l) 2,4-Pentanedione

(m) 6-Amino-3-heptanone

(n) 6-Amino-3-oxoheptanal

(o) (*S*)-2-Ethoxycyclohexanone

SECTION 12.5 Addition of Carbon Nucleophiles

12.19 Write an equation for the acid–base reaction between phenylmagnesium iodide and a carboxylic acid. Use curved arrows to show the flow of electrons in this reaction. In addition, show that the reaction is an example of a stronger acid and stronger base reacting to form a weaker acid and weaker base. **(See Example 12.4)**

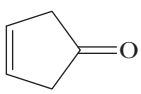
***12.20** Diethyl ether is prepared on an industrial scale by the acid-catalyzed dehydration of ethanol:

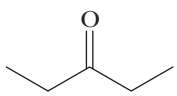
$$2CH_3CH_2OH \xrightarrow[180\ ^\circ C]{H_2SO_4} CH_3CH_2OCH_2CH_3 + H_2O$$

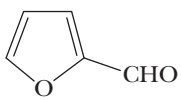
Explain why diethyl ether used in the preparation of Grignard reagents must be carefully purified to remove all traces of ethanol and water.

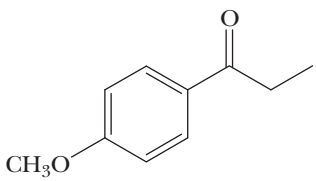
12.21 Draw structural formulas for the product formed by treating each compound with propylmagnesium bromide, followed by hydrolysis in aqueous acid: **(See Examples 12.4, 12.5)**

(a) CH_2O

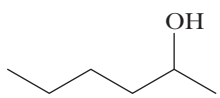
(b) 

(c) 

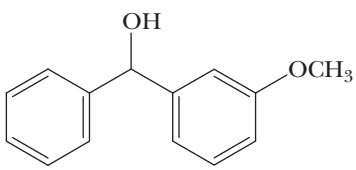
(d) 

(e) 

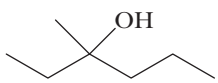
12.22 Suggest a synthesis for each alcohol, starting from an aldehyde or a ketone and an appropriate Grignard reagent (the number of combinations of Grignard reagent and aldehyde or ketone that might be used is shown in parentheses below each target molecule): **(See Examples 12.4, 12.5)**

(a) 

(Two combinations)

(b) 

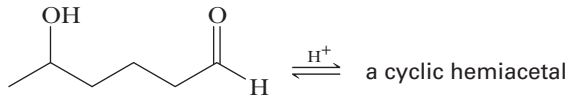
(Two combinations)

(c) 

(Three combinations)

SECTION 12.6 Addition of Oxygen Nucleophiles

12.23 5-Hydroxyhexanal forms a six-membered cyclic hemiacetal that predominates at equilibrium in aqueous solution: **(See Example 12.6)**



5-Hydroxyhexanal

(a) Draw a structural formula for this cyclic hemiacetal.

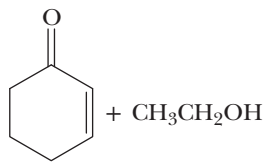
(b) How many stereoisomers are possible for 5-hydroxyhexanal?

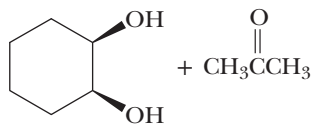
(c) How many stereoisomers are possible for the cyclic hemiacetal?

(d) Draw alternative chair conformations for each stereoisomer.

(e) For each stereoisomer, which alternative chair conformation is the more stable?

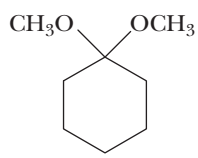
12.24 Draw structural formulas for the hemiacetal and then the acetal formed from each pair of reactants in the presence of an acid catalyst: **(See Example 12.6)**

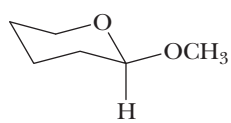
(a) 

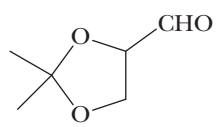
(b) 

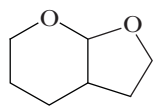
(c) 

12.25 Draw structural formulas for the products of hydrolysis of each acetal in aqueous acid: **(See Example 12.6)**

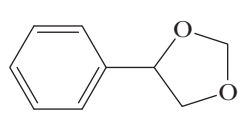
(a) 

(b) 

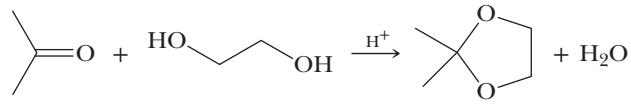
(c) 

(d) 

12.26 The following compound is a component of the fragrance of jasmine: From what carbonyl-containing compound and alcohol is the compound derived? **(See Example 12.6)**

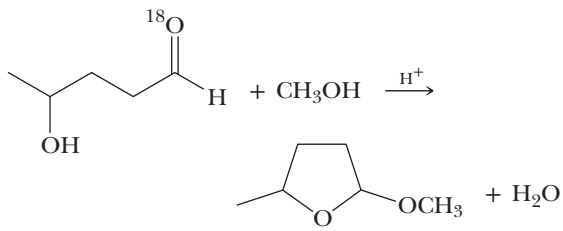


12.27 Propose a mechanism for the formation of the cyclic acetal by treating acetone with ethylene glycol in the presence of an acid catalyst. Make sure that your mechanism is consistent with the fact that the oxygen atom of the water molecule is derived from the carbonyl oxygen of acetone.



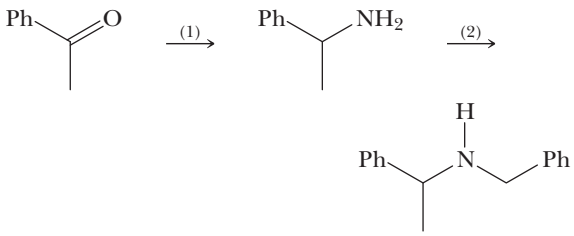
Acetone Ethylene glycol

12.28 Propose a mechanism for the formation of a cyclic acetal from 4-hydroxypentanal and one equivalent of methanol: If the carbonyl oxygen of 4-hydroxypentanal is enriched with oxygen-18, does your mechanism predict that the oxygen label appears in the cyclic acetal or in the water? Explain.

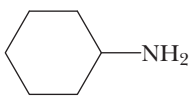


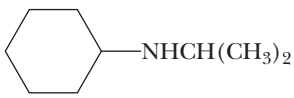
SECTION 12.7 Addition of Nitrogen Nucleophiles

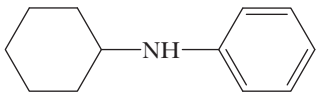
12.29 Show how this secondary amine can be prepared by two successive reductive aminations: **(See Examples 12.8, 12.9)**



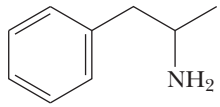
12.30 Show how to convert cyclohexanone to each of the following amines: **(See Examples 12.8, 12.9)**

(a) 

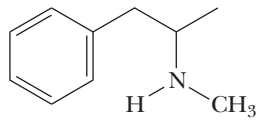
(b) 

(c) 

***12.31** Following are structural formulas for amphetamine and methamphetamine: **(See Examples 12.8, 12.9)**

(a) 

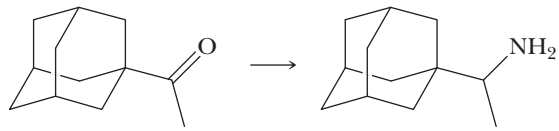
Amphetamine

(b) 

Methamphetamine

The major central nervous system effects of amphetamine and amphetaminelike drugs are locomotor stimulation, euphoria and excitement, stereotyped behavior, and anorexia. Show how each drug can be synthesized by the reductive amination of an appropriate aldehyde or ketone.

***12.32** Rimantadine was once used to prevent infections caused by the influenza A virus, but virus strains have since acquired immunity to the drug. It has, however, been used to some success in treating Parkinson's disease. Following is the final step in the synthesis of rimantadine: **(See Examples 12.8, 12.9)**

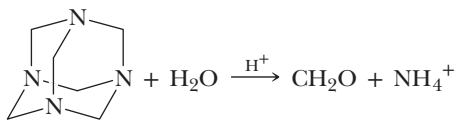


Rimantadine
(an antiviral agent)

(a) Describe experimental conditions to bring about this final step.

(b) Is rimantadine chiral?

***12.33** Methenamine, a product of the reaction of formaldehyde and ammonia, is a *prodrug*—a compound that is inactive by itself, but is converted to an active drug in the body by a biochemical transformation. The strategy behind the use of methenamine as a prodrug is that nearly all bacteria are sensitive to formaldehyde at concentrations of 20 mg/mL or higher. Formaldehyde cannot be used directly in medicine, however, because an effective concentration in plasma cannot be achieved with safe doses. Methenamine is stable at pH 7.4 (the pH of blood plasma), but undergoes acid-catalyzed hydrolysis to formaldehyde and ammonium ion under the acidic conditions of the kidneys and the urinary tract:



Methenamine

Thus, methenamine can be used as a site-specific drug to treat urinary infections.

(a) Balance the equation for the hydrolysis of methenamine to formaldehyde and ammonium ion.

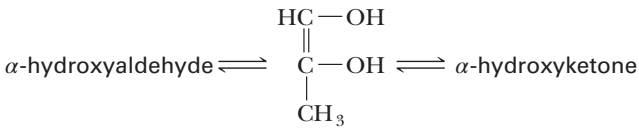
(b) Does the pH of an aqueous solution of methenamine increase, remain the same, or decrease as a result of the hydrolysis of the compound? Explain.

(c) Explain the meaning of the following statement: The functional group in methenamine is the nitrogen analog of an acetal.

(d) Account for the observation that methenamine is stable in blood plasma, but undergoes hydrolysis in the urinary tract (p*H* 6.0).

SECTION 12.8 Keto–Enol Tautomerism

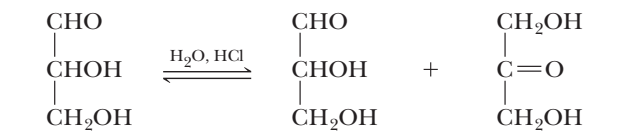
12.34 The following molecule belongs to a class of compounds called enediols: Each carbon of the double bond carries an —OH group:



An enediol

Draw structural formulas for the α-hydroxyketone and the α-hydroxyaldehyde with which this enediol is in equilibrium. **(See Example 12.10)**

12.35 In dilute aqueous acid, (*R*)-glyceraldehyde is converted into an equilibrium mixture of (*R,S*)-glyceraldehyde and dihydroxyacetone:



(*R*)-Glyceraldehyde | (*R,S*)-Glyceraldehyde | Dihydroxyacetone

Propose a mechanism for this isomerization.

SECTION 12.9 Oxidation/Reduction of Aldehydes and Ketones

12.36 Draw a structural formula for the product formed by treating butanal with each of the following sets of reagents: **(See Examples 12.11, 12.12)**

(a) $LiAlH_4$ followed by H_2O

(b) $NaBH_4$ in CH_3OH/H_2O

(c) H_2/Pt

(d) $Ag(NH_3)_2^+$ in NH_3/H_2O and then HCl/H_2O

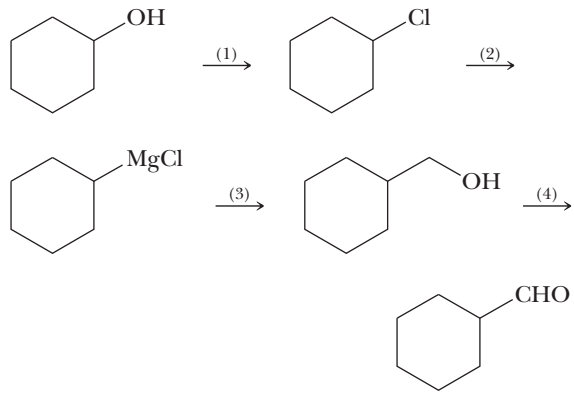
(e) H_2CrO_4

(f) $C_6H_5NH_2$ in the presence of H_2/Ni

12.37 Draw a structural formula for the product of the reaction of *p*-bromoacetophenone with each set of reagents in Problem 12.36. **(See Examples 12.11, 12.12)**

Synthesis

12.38 Show the reagents and conditions that will bring about the conversion of cyclohexanol to cyclohexanecarbaldehyde: **(See Example 12.7)**



12.39 Starting with cyclohexanone, show how to prepare these compounds (in addition to the given starting material, use any other organic or inorganic reagents, as necessary): **(See Example 12.7)**

(a) Cyclohexanol

(b) Cyclohexene

(c) Bromocyclohexane

(d) 1-Methylcyclohexanol

(e) 1-Methylcyclohexene

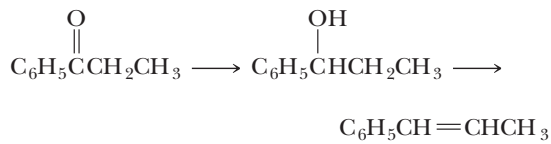
(f) 1-Phenylcyclohexanol

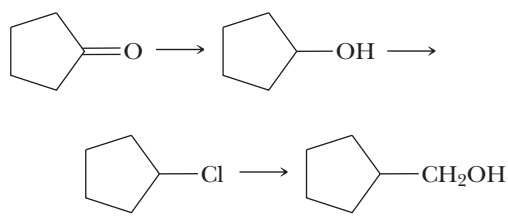
(g) 1-Phenylcyclohexene

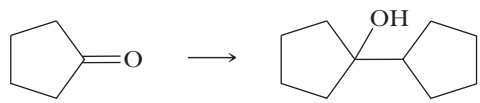
(h) Cyclohexene oxide

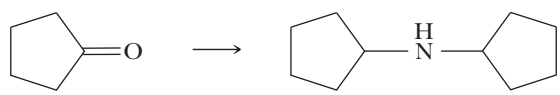
(i) *trans*-1,2-Cyclohexanediol

12.40 Show how to bring about these conversions (in addition to the given starting material, use any other organic or inorganic reagents, as necessary): **(See Example 12.7)**

(a) 

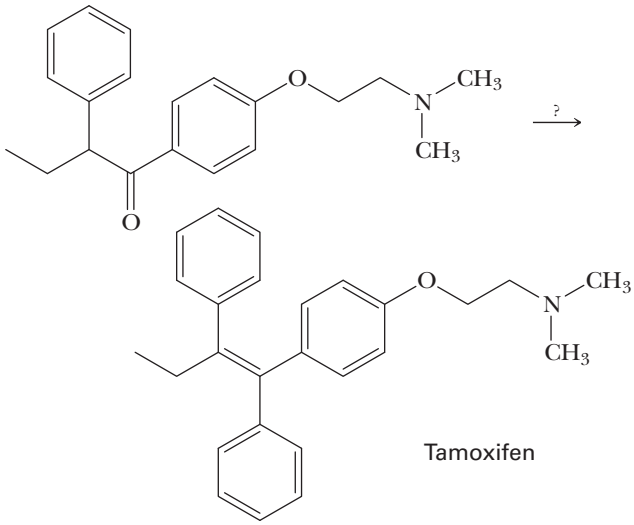
(b) 

(c) 

(d) 

***12.41** Many tumors of the breast are estrogen dependent. Drugs that interfere with estrogen binding have antitumor activity and may even help prevent the occurrence of tumors.

A widely used antiestrogen drug is tamoxifen: **(See Example 12.7)**



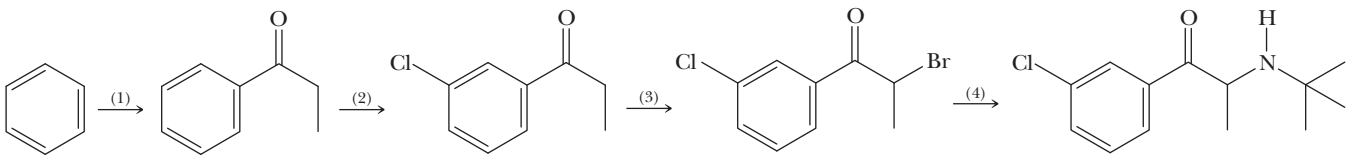
Tamoxifen

(a) How many stereoisomers are possible for tamoxifen?

(b) Specify the configuration of the stereoisomer shown here.

(c) Show how tamoxifen can be synthesized from the given ketone using a Grignard reaction, followed by dehydration.

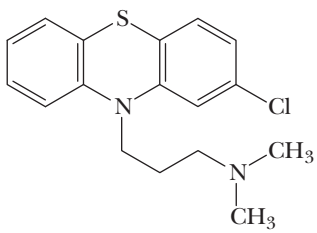
***12.42** Following is a possible synthesis of the antidepressant bupropion (Wellbutrin®): **(See Example 12.7)**



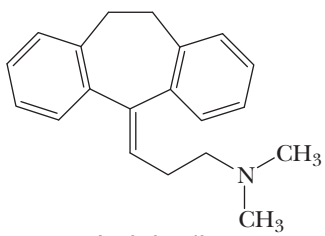
Bupropion
(Wellbutrin®)

Show the reagents that will bring about each step in this synthesis.

***12.43** The synthesis of chlorpromazine in the 1950s and the discovery soon thereafter of the drug's antipsychotic activity opened the modern era of biochemical investigations into the pharmacology of the central nervous system. One of the compounds prepared in the search for more effective antipsychotics was amitriptyline. **(See Example 12.7)**

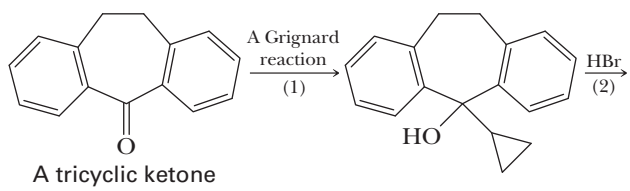


Chlorpromazine

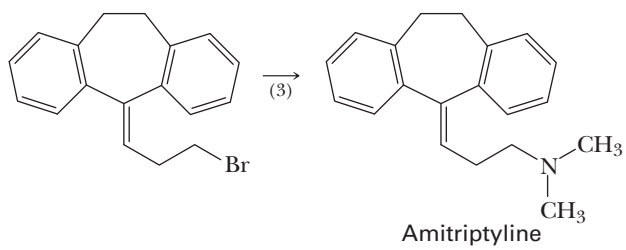


Amitriptyline

Surprisingly, amitriptyline shows antidepressant activity rather than antipsychotic activity. It is now known that amitriptyline inhibits the reuptake of norepinephrine and serotonin from the synaptic cleft. Because the reuptake of these neurotransmitters is inhibited, their effects are potentiated. That is, the two neurotransmitters remain available to interact with serotonin and norepinephrine receptor sites longer and continue to cause excitation of serotonin and norepinephrine-mediated neural pathways. The following is a synthesis for amitriptyline:



A tricyclic ketone



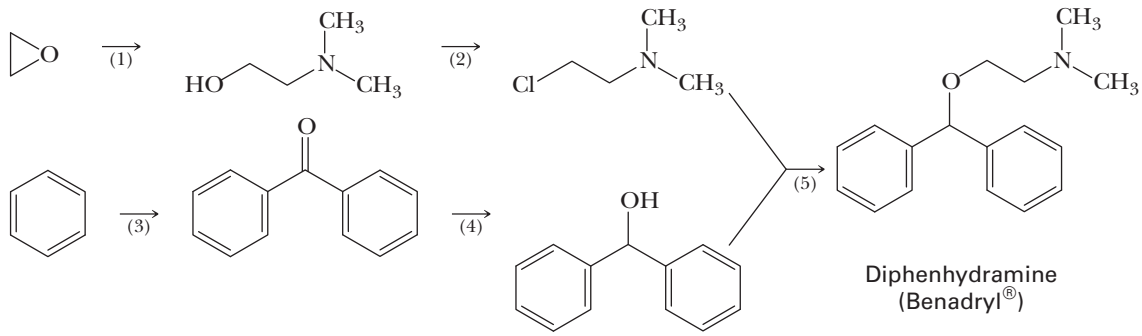
Amitriptyline

(a) Propose a reagent for Step 1.

(b) Propose a mechanism for Step 2. (*Note:* It is not acceptable to propose a primary carbocation as an intermediate.)

(c) Propose a reagent for Step 3.

***12.44** Following is a synthesis for diphenhydramine: **(See Example 12.7)**



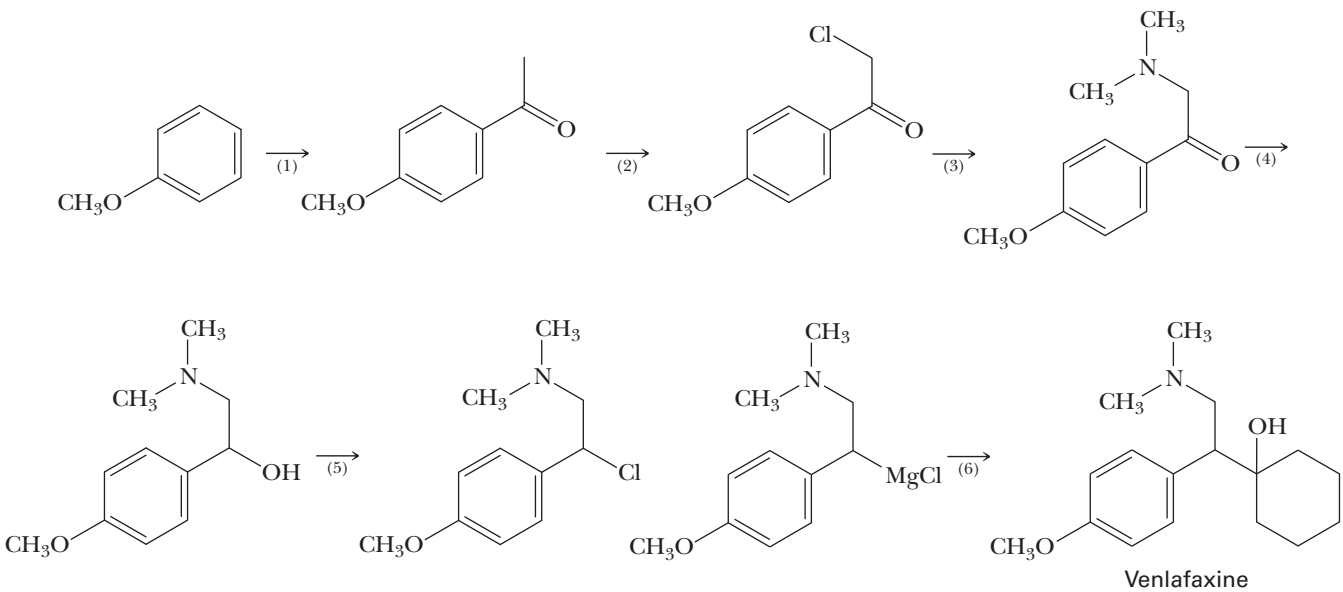
The hydrochloride salt of this compound, best known by its trade name, Benadryl®, is an antihistamine.

(a) Propose reagents for Steps 1 and 2.

(b) Propose reagents for Steps 3 and 4.

(c) Show that Step 5 is an example of nucleophilic aliphatic substitution. What type of mechanism — S_N1 or S_N2 — is more likely for this reaction? Explain.

***12.45** Following is a synthesis for the antidepressant venlafaxine: **(See Example 12.7)**



(a) Propose a reagent for Step 1, and name the type of reaction that takes place.

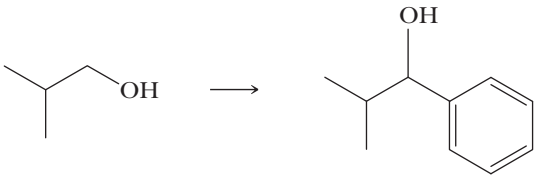
(b) Propose reagents for Steps 2 and 3.

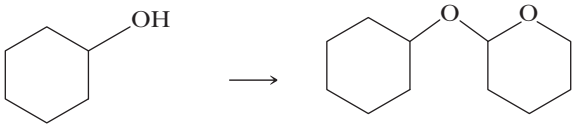
(c) Propose reagents for Steps 4 and 5.

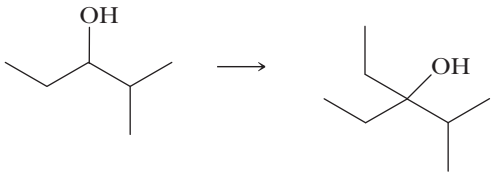
(d) Propose a reagent for Step 6, and name the type of reaction that takes place.

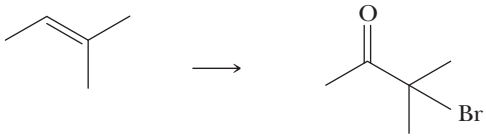
CHEMICAL TRANSFORMATIONS

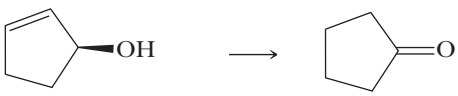
12.46 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note*: Some will require more than one step.

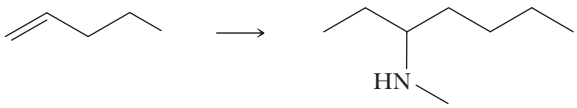
(a) 

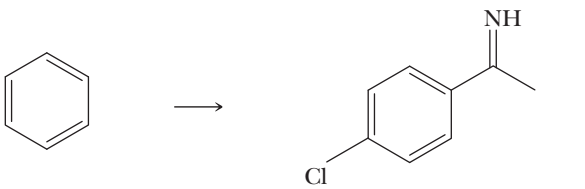
(b) 

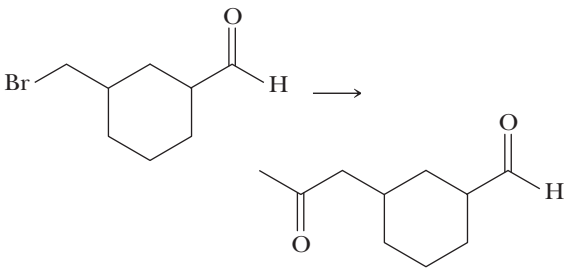
(c) 

(d) 

(e) 

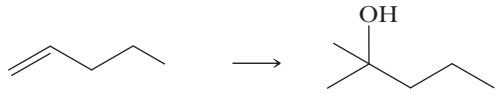
(f) 

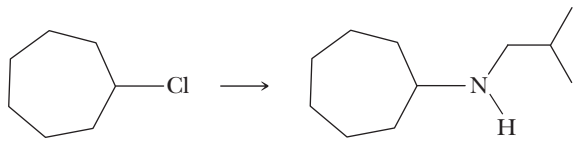
(g) 

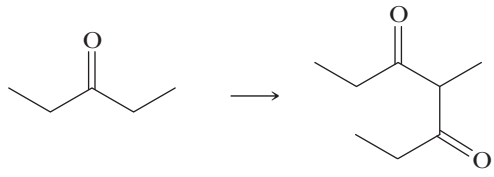
(h) 

(i) 

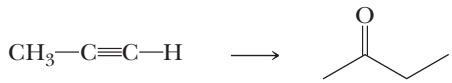
(j) 

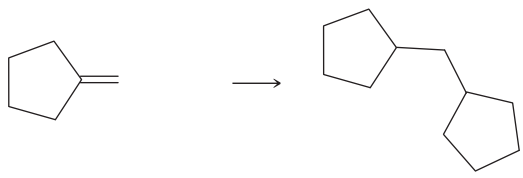
(k) 

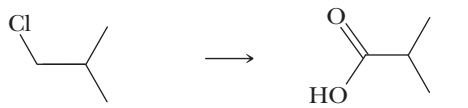
(l) 

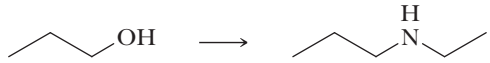
(m) 

(n) 

(o) 

(p) 

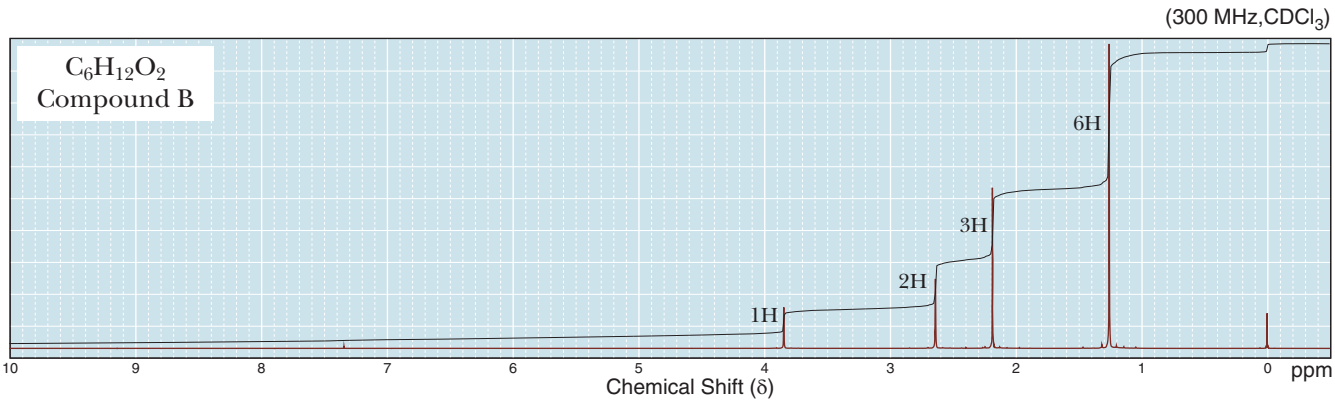
(q) 

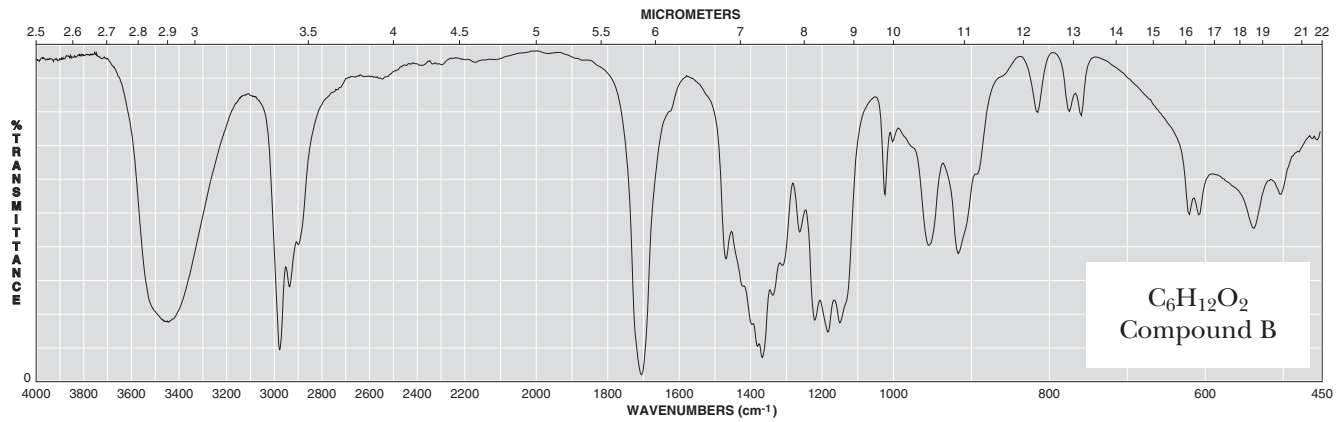
(r) 

SPECTROSCOPY

12.47 Compound A, $C_5H_{10}O$, is used as a flavoring agent for many foods that possess a chocolate or peach flavor. Its common name is isovaleraldehyde, and it gives ^{13}C-NMR peaks at δ 202.7, 52.7, 23.6, and 22.6. Provide a structural formula for isovaleraldehyde and give its IUPAC name.

12.48 Following are ^{1}H-NMR and IR spectra of compound B, $C_6H_{12}O_2$:



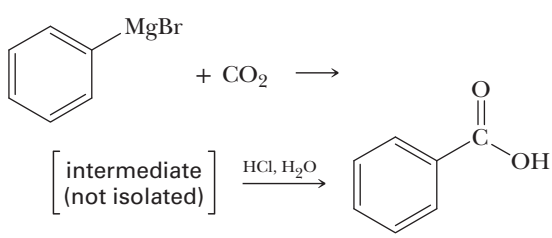


Propose a structural formula for compound B.

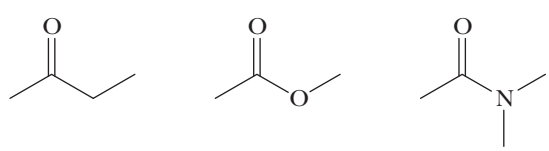
12.49 Compound C, $C_9H_{18}O$, is used in the automotive industry to retard the flow of solvent and thus improve the application of paints and coatings. It yields ^{13}C-NMR peaks at δ 210.5, 52.4, 24.5, and 22.6. Provide a structure and an IUPAC name for compound C.

LOOKING AHEAD

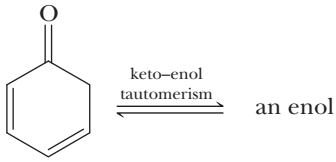
12.50 Reaction of a Grignard reagent with carbon dioxide, followed by treatment with aqueous HCl, gives a carboxylic acid. Propose a structural formula for the bracketed intermediate formed by the reaction of phenylmagnesium bromide with CO_2, and propose a mechanism for the formation of this intermediate:



12.51 Rank the following carbonyls in order of increasing reactivity to nucleophilic attack, and explain your reasoning.

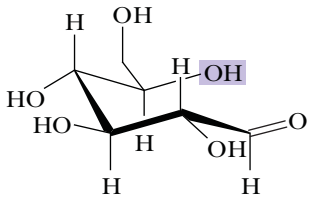


12.52 Provide the enol form of this ketone and predict the direction of equilibrium:



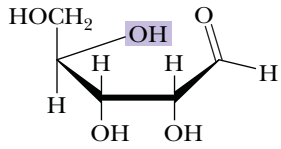
12.53 Draw the cyclic hemiacetal formed by reaction of the highlighted —OH group with the aldehyde group:

(a)



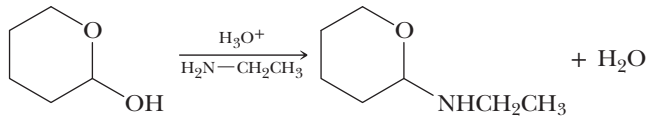
Glucose

(b)



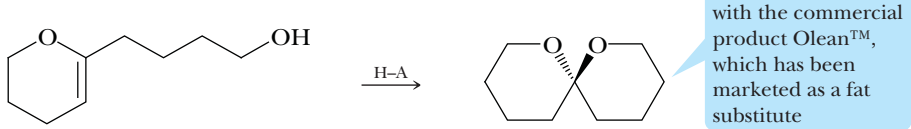
Ribose

12.54 Propose a mechanism for the acid-catalyzed reaction of the following hemiacetal, with an amine acting as a nucleophile:



GROUP LEARNING ACTIVITIES

12.55 Pheromones are important organic compounds in agriculture because they represent one means of baiting and trapping insects that may be harmful to crops. Olean, the sex pheromone for the olive fruit fly, *Dacus oleae*, can be synthesized from the hydroxyenol ether shown by treating it with a Brønsted acid (H–A).



Olean

not to be confused with the commercial product Olean™, which has been marketed as a fat substitute

As a group, answer the following questions related to this agriculturally important product:

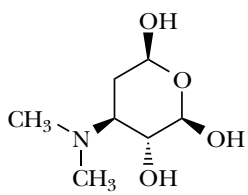
(a) Name the functional group in Olean.

(b) Propose a mechanism for the reaction. *Hint:* The mechanism consists of the following patterns: (1) add a proton, (2) reaction of an electrophile and a nucleophile to form a new covalent bond, and (3) take a proton away.

(c) Is Olean chiral? If so, how many stereoisomers are possible? *Hint:* Build a model of olean. Then build a second model in which the two central C—O bonds are swapped.

(d) Predict the product formed by acid-catalyzed hydrolysis of Olean.

***12.56** Following is a structural formula of desosamine, a sugar component of several macrolide antibiotics, including the erythromycins (Problem 8.57). The configuration shown here is that of the natural product.



Desosamine

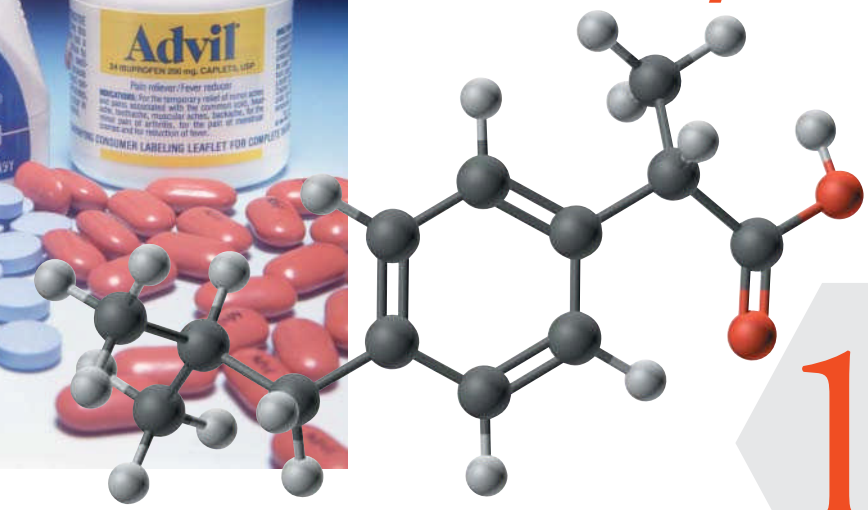
(a) How many stereoisomers are possible?

(b) Can you spot the hemiacetals or acetals? For each that you spot, show the structure of the ketone or aldehyde and the alcohols from which it can be derived.

(c) Draw alternative chair conformations for desosamine and label groups on the ring as either axial or equatorial.

(d) Which of the alternative chair conformations is the more stable?

Carboxylic Acids



Charles D. Winters

The active ingredients in these two over-the-counter pain relievers are derivatives of arylpropanoic acids. See Chemical Connections 13A, "From Willow Bark to Aspirin and Beyond." Inset: A model of (*S*)-ibuprofen.

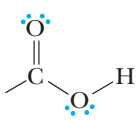
13

THE NEXT TIME YOU take an aspirin (acetylsalicylic acid) or drink milk (contains lactic acid), you might be reminded of carboxylic acids, another class of organic compounds containing the carbonyl group. Their occurrence in nature is widespread, and they are important components of foodstuffs such as vinegar, butter, and vegetable oils. The most important chemical property of carboxylic acids is their acidity. Furthermore, carboxylic acids form numerous important derivatives, including esters, amides, anhydrides, and acid halides. In this chapter, we study carboxylic acids themselves; in Chapters 14 and 15, we study their derivatives.

13.1 What Are Carboxylic Acids?

The functional group of a carboxylic acid is a **carboxyl group**, so named because it is made up of a **carb**onyl group and a hydr**oxyl** group (Section 1.7D). Following is a Lewis structure of the carboxyl group, as well as two alternative representations of it:

Carboxyl group A —COOH group.



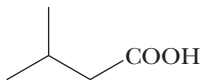
—COOH —CO_2H

The general formula of an aliphatic carboxylic acid is RCOOH; that of an aromatic carboxylic acid is ArCOOH.

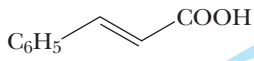
13.2 How Are Carboxylic Acids Named?

A. IUPAC System

We derive the IUPAC name of a carboxylic acid from that of the longest carbon chain that contains the carboxyl group by dropping the final *-e* from the name of the parent alkane and adding the suffix *-oic*, followed by the word *acid* (Section 3.5). We number the chain beginning with the carbon of the carboxyl group. Because the carboxyl carbon is understood to be carbon 1, there is no need to give it a number. If the carboxylic acid contains a carbon–carbon double bond, we change the infix from *-an-* to *-en-* to indicate the presence of the double bond, and we show the location of the double bond by a number. In the following examples, the common name of each acid is given in parentheses:



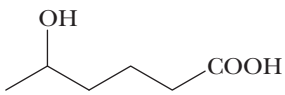
3-Methylbutanoic acid
(Isovaleric acid)



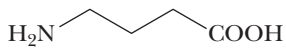
trans-3-Phenylpropenoic acid
(Cinnamic acid)

it is not necessary to indicate that the alkene occurs at position 2 because there is no other position where it can occur in this molecule

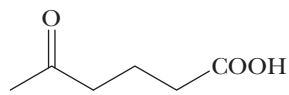
In the IUPAC system, a carboxyl group takes precedence over most other functional groups (Table 12.1), including hydroxyl and amino groups, as well as the carbonyl groups of aldehydes and ketones. As illustrated in the following examples, an —OH group of an alcohol is indicated by the prefix *hydroxy-*, an $—NH_2$ group of an amine by *amino-*, and an =O group of an aldehyde or ketone by *oxo-*:



5-Hydroxyhexanoic acid

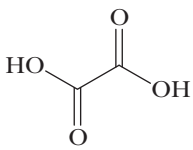


4-Aminobutanoic acid

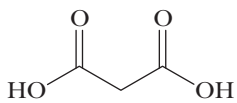


5-Oxohexanoic acid

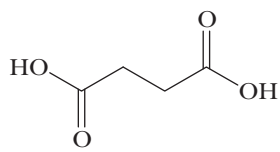
Dicarboxylic acids are named by adding the suffix *-dioic*, followed by the word *acid*, to the name of the carbon chain that contains both carboxyl groups. Because the two carboxyl groups can be only at the ends of the parent chain, there is no need to number them. Following are IUPAC names and common names for several important aliphatic dicarboxylic acids:



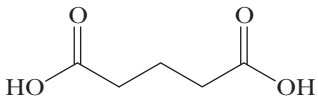
Ethanedioic acid
(Oxalic acid)



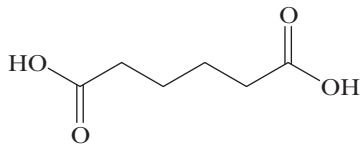
Propanedioic acid
(Malonic acid)



Butanedioic acid
(Succinic acid)



Pentanedioic acid
(Glutaric acid)



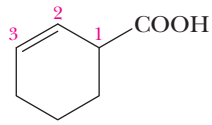
Hexanedioic acid
(Adipic acid)

lenetstan/Shutterstock

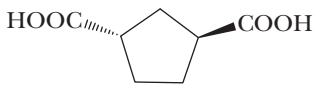
The fibers of this rope are made from nylon 66, a material synthesized from adipic acide.

The name *oxalic acid* is derived from one of its sources in the biological world, namely, plants of the genus *Oxalis*, one of which is rhubarb. Oxalic acid also occurs in human and animal urine, and calcium oxalate (the calcium salt of oxalic acid) is a major component of kidney stones. Adipic acid is one of the two monomers required for the synthesis of the polymer nylon 66. The U.S. chemical industry produces approximately 1.8 billion pounds of adipic acid annually, solely for the synthesis of nylon 66 (Section 16.4A).

A carboxylic acid containing a carboxyl group bonded to a cycloalkane ring is named by giving the name of the ring and adding the suffix *-carboxylic acid*. The atoms of the ring are numbered beginning with the carbon bearing the —COOH group:



2-Cyclohexenecarboxylic acid



trans-1,3-Cyclopentanedicarboxylic acid

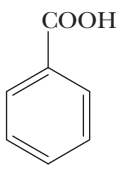
Lisa Kyle Young/Getty Images, Inc.

Leaves of the rhubarb plant contain oxalic acid as its potassium and sodium salts.

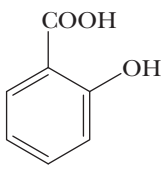
The simplest aromatic carboxylic acid is benzoic acid. Derivatives are named by using numbers and prefixes to show the presence and location of substituents relative to the carboxyl group. Certain aromatic carboxylic acids have common names by which they are more usually known. For example, 2-hydroxybenzoic acid is more often called salicylic acid, a name derived from the fact that this aromatic carboxylic acid was first obtained from the bark of the willow, a tree of the genus *Salix*. Aromatic dicarboxylic acids are named by adding the words *dicarboxylic acid* to *benzene*. Examples are 1,2-benzenedicarboxylic acid and 1,4-benzenedicarboxylic acid. Each is more usually known by its common name: phthalic acid and terephthalic acid, respectively. Terephthalic acid is one of the two organic components required for the synthesis of the textile fiber known as Dacron® polyester (Section 16.4B).

K. Miri Photography/ Shutterstock

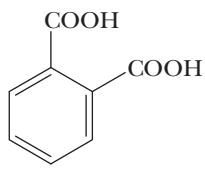
Dacron is a plastic fiber made from terephthalic acid and commonly used as stuffing for pillows.



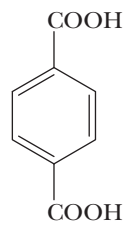
Benzoic acid



2-Hydroxybenzoic acid (Salicylic acid)



1,2-Benzenedicarboxylic acid (Phthalic acid)

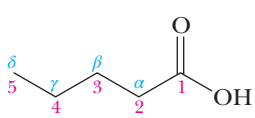


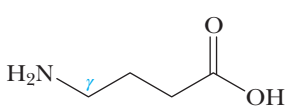
1,4-Benzenedicarboxylic acid (Terephthalic acid)

B. Common Names

Aliphatic carboxylic acids, many of which were known long before the development of structural theory and IUPAC nomenclature, are named according to their source or for some characteristic property. Table 13.1 lists several of the unbranched aliphatic carboxylic acids found in the biological world, along with the common name of each. Those with 16, 18, and 20 carbon atoms are particularly abundant in fats and oils (Section 19.1) and the phospholipid components of biological membranes (Section 19.3).

When common names are used, the Greek letters α, β, γ, δ, and so forth are often added as a prefix to locate substituents. The α-position in a carboxylic acid is the position next to the carboxyl group; an α-substituent in a common name is equivalent to a 2-substituent in an IUPAC name. *GABA*, short for *g*amma-*a*mino*b*utyric *a*cid, is an inhibitory neurotransmitter in the central nervous system of humans:





4-Aminobutanoic acid (γ-Aminobutyric acid, GABA)

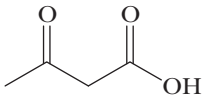
Fotosearch RF/Getty Images, Inc.

Formic acid was first obtained in 1670 from the destructive distillation of ants, whose genus is *Formica*. It is one of the components of the venom of stinging ants.

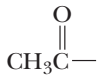
TABLE 13.1 Several Aliphatic Carboxylic Acids and Their Common Names

Structure	IUPAC Name	Common Name	Derivation
$HCOOH$	Methanoic acid	Formic acid	Latin: *formica*, ant
CH_3COOH	Ethanoic acid	Acetic acid	Latin: *acetum*, vinegar
CH_3CH_2COOH	Propanoic acid	Propionic acid	Greek: *propion*, first fat
$CH_3(CH_2)_2COOH$	Butanoic acid	Butyric acid	Latin: *butyrum*, butter
$CH_3(CH_2)_3COOH$	Pentanoic acid	Valeric acid	Latin: *valere*, to be strong
$CH_3(CH_2)_4COOH$	Hexanoic acid	Caproic acid	Latin: *caper*, goat
$CH_3(CH_2)_6COOH$	Octanoic acid	Caprylic acid	Latin: *caper*, goat
$CH_3(CH_2)_8COOH$	Decanoic acid	Capric acid	Latin: *caper*, goat
$CH_3(CH_2)_{10}COOH$	Dodecanoic acid	Lauric acid	Latin: *laurus*, laurel
$CH_3(CH_2)_{12}COOH$	Tetradecanoic acid	Myristic acid	Greek: *myristikos*, fragrant
$CH_3(CH_2)_{14}COOH$	Hexadecanoic acid	Palmitic acid	Latin: *palma*, palm tree
$CH_3(CH_2)_{16}COOH$	Octadecanoic acid	Stearic acid	Greek: *stear*, solid fat
$CH_3(CH_2)_{18}COOH$	Icosanoic acid	Arachidic acid	Greek: *arachis*, peanut

In common nomenclature, the prefix *keto-* indicates the presence of a ketone carbonyl in a substituted carboxylic acid (as illustrated by the common name β-ketobutyric acid):



3-Oxobutanoic acid (β-Ketobutyric acid; Acetoacetic acid)



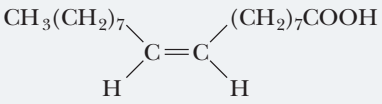
Acetyl group (Aceto group)

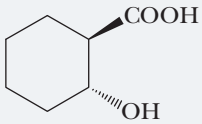
Aceto group A $CH_3C(=O)-$ group.

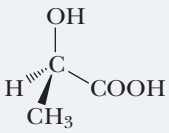
An alternative common name for 3-oxobutanoic acid is acetoacetic acid. In deriving this common name, this ketoacid is regarded as a substituted acetic acid, and the $CH_3C(=O)-$ substituent is named an **aceto group**.

EXAMPLE 13.1

Write the IUPAC name for each carboxylic acid:

(a) 

(b) 

(c) 

(d) $ClCH_2COOH$

STRATEGY

Identify the longest chain of carbon atoms that contains the carboxyl group to determine the root name. The suffix *-e* is then changed to *-anoic acid*. For cyclic carboxylic acids, *carboxylic acid* is appended to the name of the cycloalkane (without dropping the suffix *-e*). As usual, remember to note stereochemistry (*E/Z*, *cis/trans*, or *R/S*) where appropriate.

SOLUTION

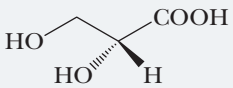
Given first are IUPAC names and then, in parentheses, common names:

(a) *cis*-9-Octadecenoic acid (oleic acid)
(b) *trans*-2-Hydroxycyclohexanecarboxylic acid
(c) (*R*)-2-Hydroxypropanoic acid [(*R*)-lactic acid]
(d) Chloroethanoic acid (chloroacetic acid)

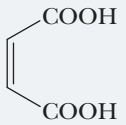
See problems 13.9–13.12, 13.15

PROBLEM 13.1

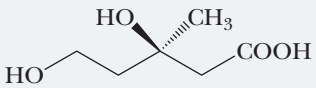
Each of the following compounds has a well-recognized common name. A derivative of glyceric acid is an intermediate in glycolysis (Section 21.3). Maleic acid is an intermediate in the tricarboxylic acid (TCA) cycle. Mevalonic acid is an intermediate in the biosynthesis of steroids (Section 19.4B). Lactic acid is a product of fermentation in animals (Section 21.4A).

(a) 

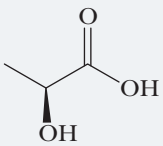
Glyceric acid

(b) 

Maleic acid

(c) 

Mevalonic acid

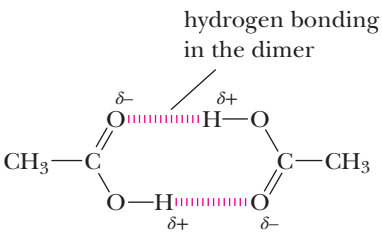
(d) 

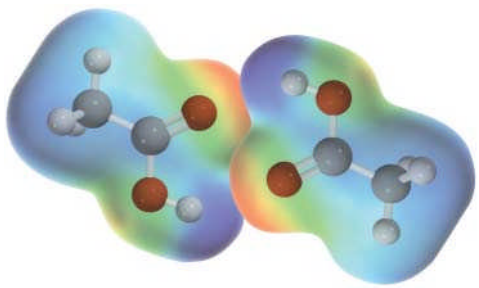
Lactic acid

Write the IUPAC name for each compound. Be certain to show the configuration of each.

13.3 What Are the Physical Properties of Carboxylic Acids?

In the liquid and solid states, carboxylic acids are associated by intermolecular hydrogen bonding into dimers, as shown for acetic acid:





Carboxylic acids have significantly higher boiling points than other types of organic compounds of comparable molecular weight, such as alcohols, aldehydes, and ketones. For example, butanoic acid (Table 13.2) has a higher boiling point than either 1-pentanol or pentanal. The higher boiling points of carboxylic acids result from their polarity and from the fact that they form very strong intermolecular hydrogen bonds.

Carboxylic acids also interact with water molecules by hydrogen bonding through both their carbonyl and hydroxyl groups. Because of these hydrogen-bonding interactions,

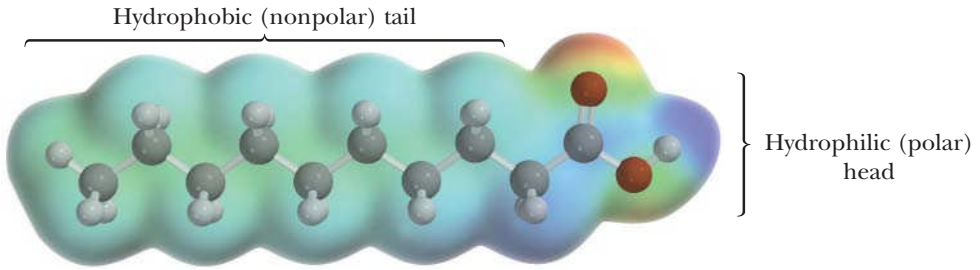
TABLE 13.2 Boiling Points and Solubilities in Water of Selected Carboxylic Acids, Alcohols, and Aldehydes of Comparable Molecular Weight

Structure	Name	Molecular Weight	Boiling Point (°C)	Solubility (g/100 mL H_2O)
CH_3COOH	acetic acid	60.5	118	infinite
$CH_3CH_2CH_2OH$	1-propanol	60.1	97	infinite
CH_3CH_2CHO	propanal	58.1	48	16
$CH_3(CH_2)_2COOH$	butanoic acid	88.1	163	infinite
$CH_3(CH_2)_3CH_2OH$	1-pentanol	88.1	137	2.3
$CH_3(CH_2)_3CHO$	pentanal	86.1	103	slight
$CH_3(CH_2)_4COOH$	hexanoic acid	116.2	205	1.0
$CH_3(CH_2)_5CH_2OH$	1-heptanol	116.2	176	0.2
$CH_3(CH_2)_5CHO$	heptanal	114.1	153	0.1

carboxylic acids are more soluble in water than are alcohols, ethers, aldehydes, and ketones with comparable molecular weight. The solubility of a carboxylic acid in water decreases as its molecular weight increases. We account for this trend in the following way: A carboxylic acid consists of two regions of different polarity—a polar, hydrophilic carboxyl group and, except for formic acid, a nonpolar, hydrophobic hydrocarbon chain. The **hydrophilic** carboxyl group increases water solubility; the **hydrophobic** hydrocarbon chain decreases water solubility.

Hydrophilic From the Greek, meaning "water loving."

Hydrophobic From the Greek, meaning "water hating."



Decanoic acid
(0.2 g/100 mL H_2O)

The first four aliphatic carboxylic acids (formic, acetic, propanoic, and butanoic acids) are infinitely soluble in water because the hydrophilic character of the carboxyl group more than counterbalances the hydrophobic character of the hydrocarbon chain. As the size of the hydrocarbon chain increases relative to the size of the carboxyl group, water solubility decreases. The solubility of hexanoic acid in water is 1.0 g/100 g water; that of decanoic acid is only 0.2 g/100 g water.

One other physical property of carboxylic acids must be mentioned: The liquid carboxylic acids, from propanoic acid to decanoic acid, have extremely foul odors, about as bad as those of thiols, though different. Butanoic acid is found in stale perspiration and is a major component of "locker room odor." Pentanoic acid smells even worse, and goats, which secrete C_6, C_8, and C_{10} acids, are not famous for their pleasant odors.

13.4 What Are the Acid–Base Properties of Carboxylic Acids?

A. Acid Ionization Constants

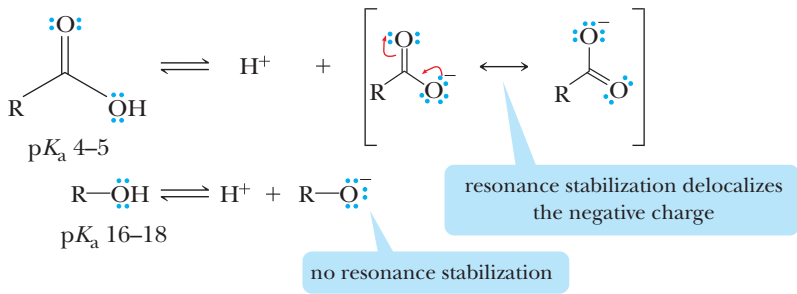
Carboxylic acids are weak acids. Values of K_a for most unsubstituted aliphatic and aromatic carboxylic acids fall within the range from 10^{-4} to 10^{-5}. The value of K_a for acetic acid, for example, is 1.74×10^{-5}, and the pK_a of acetic acid is 4.76:

$$CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$$

$$K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.74 \times 10^{-5}$$

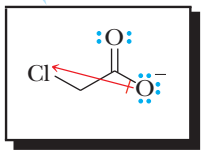
$$pK_a = 4.76$$

As we discussed in Section 2.5B, carboxylic acids (pK_a 4–5) are stronger acids than alcohols (pK_a 16–18) because resonance stabilizes the **carboxylate** anion by delocalizing its negative charge. No comparable resonance stabilization exists in alkoxide ions.



Substitution at the α-carbon of an atom or a group of atoms with higher electronegativity than carbon increases the acidity of carboxylic acids, often by several orders of magnitude (Section 2.5C). Compare, for example, the acidities of acetic acid (pK_a 4.76) and chloroacetic acid (pK_a 2.86). A single chlorine substituent on the α-carbon increases acid strength by nearly 100! Both dichloroacetic acid and trichloroacetic acid are stronger acids than phosphoric acid (pK_a 2.1):

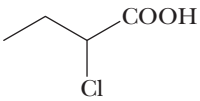
the inductive effect of an electronegative atom delocalizes the negative charge and stabilizes the carboxylate ion



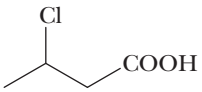
Formula:	CH_3COOH	$ClCH_2COOH$	$Cl_2CHCOOH$	Cl_3CCOOH
Name:	Acetic acid	Chloroacetic acid	Dichloroacetic acid	Trichloroacetic acid
pK_a:	4.76	2.86	1.48	0.70

Increasing acid strength

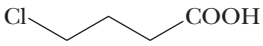
The acid-strengthening effect of halogen substitution falls off rather rapidly with increasing distance from the carboxyl group. Although the acid ionization constant for 2-chlorobutanoic acid (pK_a 2.83) is 100 times that for butanoic acid, the acid ionization constant for 4-chlorobutanoic acid (pK_a 4.52) is only about twice that for butanoic acid:



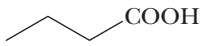
2-Chlorobutanoic acid (pK_a 2.83)



3-Chlorobutanoic acid (pK_a 3.98)



4-Chlorobutanoic acid (pK_a 4.52)



Butanoic acid (pK_a 4.82)

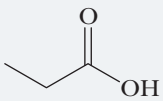
the further the halogen is from the carboxyl group, the lower is its effect on the acidity

Decreasing acid strength

EXAMPLE 13.2

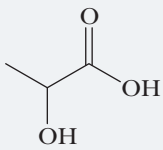
Which acid in each set is the stronger?

(a)



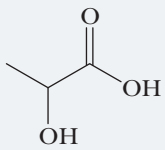
Propanoic acid

or



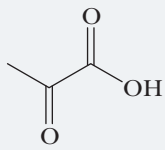
2-Hydroxypropanoic acid (Lactic acid)

(b)



2-Hydroxypropanoic acid (Lactic acid)

or



2-Oxopropanoic acid (Pyruvic acid)

STRATEGY

Draw the conjugate base of each acid and look for possible stabilization of the ion via resonance or inductive effects. The conjugate base that is more greatly stabilized will indicate the more acidic carboxylic acid.

SOLUTION

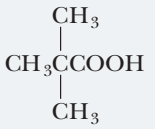
(a) 2-Hydroxypropanoic acid (pK_a 3.85) is a stronger acid than propanoic acid (pK_a 4.87) because of the electron-withdrawing inductive effect of the hydroxyl oxygen.

(b) 2-Oxopropanoic acid (pK_a 2.06) is a stronger acid than 2-hydroxypropanoic acid (pK_a 3.08) because of the greater electron-withdrawing inductive effect of the carbonyl oxygen compared with that of the hydroxyl oxygen.

See problems 13.20–13.22, 13.48

PROBLEM 13.2

Match each compound with its appropriate pK_a value:



2,2-Dimethylpropanoic acid

Trifluoroacetic acid

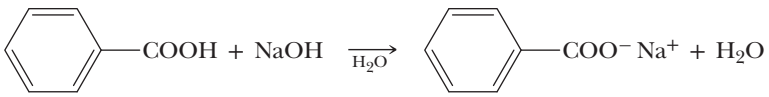
2-Hydroxypropanoic acid (Lactic acid)

pK_a values= 5.03, 3.85, and 0.22.

Sodium benzoate is a common preservative, seen here in the ingredients for a medical treatment.

B. Reaction with Bases

All carboxylic acids, whether soluble or insoluble in water, react with NaOH, KOH, and other strong bases to form water-soluble salts:

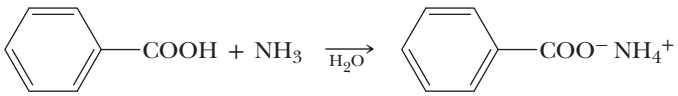


Benzoic acid (slightly soluble in water)

Sodium benzoate (60 g/100 mL water)

Sodium benzoate, a fungal growth inhibitor, is often added to packaged foods "to retard spoilage." Calcium propanoate is used for the same purpose.

Carboxylic acids also form water-soluble salts with ammonia and amines:



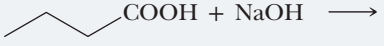
Benzoic acid (slightly soluble in water)

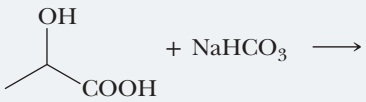
Ammonium benzoate (20 g/100 mL water)

Salts of carboxylic acids are named in the same manner as are salts of inorganic acids: Name the cation first and then the anion. Derive the name of the anion from the name of the carboxylic acid by dropping the suffix *-ic acid* and adding the suffix *-ate*. For example, the name of $CH_3CH_2COO^-Na^+$ is sodium propanoate, and that of $CH_3(CH_2)_{14}COO^-Na^+$ is sodium hexadecanoate (sodium palmitate).

EXAMPLE 13.3

Complete each acid–base reaction and name the salt formed:

(a) 

(b) 

STRATEGY

Identify the base and the most acidic hydrogen of the acid. Remember that sodium bicarbonate ($NaHCO_3$) typically reacts to yield carbonic acid, which subsequently decomposes to give CO_2 and H_2O.

SOLUTION

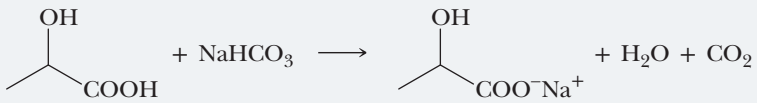
Each carboxylic acid is converted to its sodium salt. In (b), carbonic acid is formed (not shown) and decomposes to carbon dioxide and water:

(a) 

Butanoic acid

Sodium butanoate

(b)



2-Hydroxypropanoic acid (Lactic acid)

Sodium 2-hydroxypropanoate (Sodium lactate)

See problems 13.23, 13.34

PROBLEM 13.3

Write an equation for the reaction of each acid in Example 13.3 with ammonia, and name the salt formed.

A consequence of the water solubility of carboxylic acid salts is that we can convert water-insoluble carboxylic acids to water-soluble alkali metal or ammonium salts and then extract them into aqueous solution. In turn, we can transform the salt into the free carboxylic acid by adding HCl, H_2SO_4, or some other strong acid. These reactions allow us to separate water-insoluble carboxylic acids from water-insoluble neutral compounds.

Figure 13.1 shows a flowchart for the separation of benzoic acid, a water-insoluble carboxylic acid, from benzyl alcohol, a water-insoluble nonacidic compound. First, we dissolve the mixture of benzoic acid and benzyl alcohol in diethyl ether. Next, we shake the ether solution with aqueous NaOH to convert benzoic acid to its water-soluble sodium salt. Then we separate the ether from the aqueous phase. Distillation of the ether solution yields first diethyl ether (bp 35 °C) and then benzyl alcohol (bp 205 °C). When we acidify the

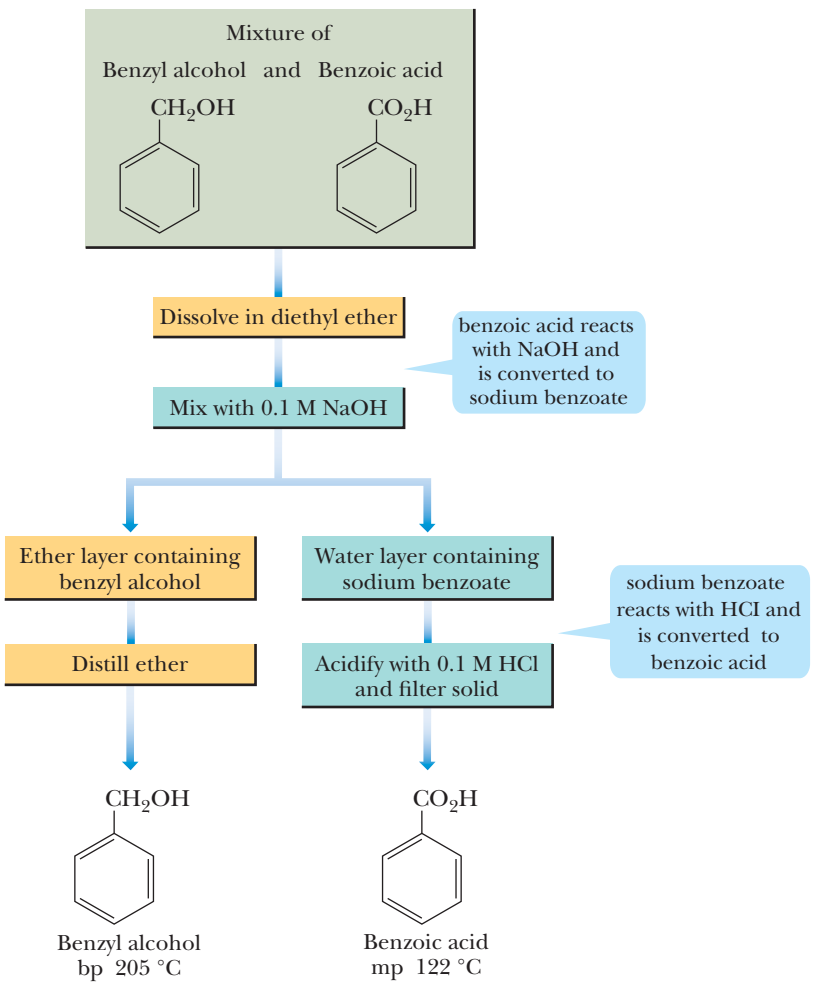


FIGURE 13.1 Flowchart for separation of benzoic acid from benzyl alcohol.

aqueous solution with HCl, benzoic acid precipitates as a water-insoluble solid (mp 122 °C) and is recovered by filtration. The ability to separate compounds based on their acid–base properties is very important in laboratory and industrial chemistry.

13.5 How Are Carboxyl Groups Reduced?

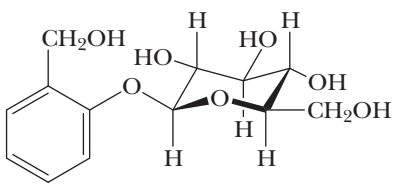
The carboxyl group is one of the organic functional groups that is most resistant to reduction. It is not affected by catalytic reduction (H_2/M) under conditions that easily reduce aldehydes and ketones to alcohols and that reduce alkenes to alkanes. The most common reagent for the reduction of a carboxyl group to a primary alcohol is the very powerful reducing agent lithium aluminum hydride (Section 12.10).

Chemical Connections 13A

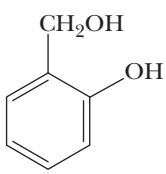
FROM WILLOW BARK TO ASPIRIN AND BEYOND

The first drug developed for widespread use was aspirin, today's most common pain reliever. Worldwide, approximately 100 billion tablets of aspirin are consumed every year! The story of the development of this modern pain reliever goes back more than 2,000 years: In 400 B.C.E., the Greek physician Hippocrates recommended chewing bark of the willow tree to alleviate the pain of childbirth and to treat eye infections.

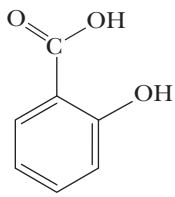
The active component of willow bark was found to be salicin, a compound composed of salicyl alcohol joined to a unit of β-D-glucose (Section 17.2). Hydrolysis of salicin in aqueous acid gives salicyl alcohol, which can then be oxidized to salicylic acid, an even more effective reliever of pain, fever, and inflammation than salicin and one without its extremely bitter taste:



Salicin



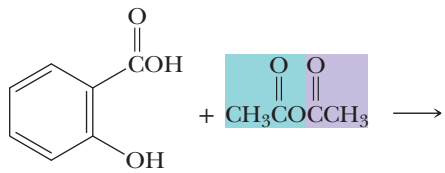
Salicyl alcohol



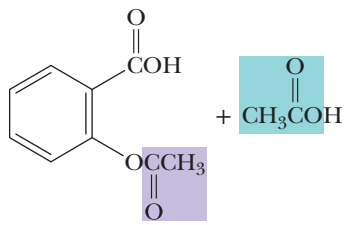
Salicylic acid

Unfortunately, patients quickly recognized salicylic acid's major side effect: It causes severe irritation of the mucous membrane lining the stomach.

In the search for less irritating, but still effective, derivatives of salicylic acid, chemists at the Bayer division of I. G. Farben in Germany prepared acetylsalicylic acid in 1883 and gave it the name *aspirin*, a word derived from the German *spirsäure* (salicylic acid), with the initial *a* for the acetyl group:



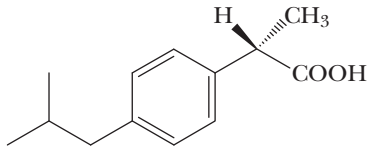
Salicylic acid — Acetic anhydride



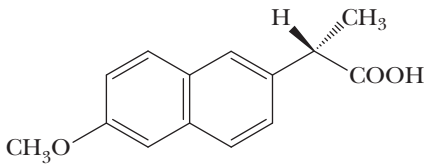
Acetyl salicylate (Aspirin)

Aspirin proved to be less irritating to the stomach than salicylic acid and also more effective in relieving the pain and inflammation of rheumatoid arthritis. Bayer began large-scale production of aspirin in 1899.

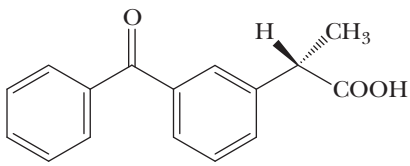
In the 1960s, in a search for even more effective and less irritating analgesics and anti-inflammatory drugs, the Boots Pure Drug Company in England studied compounds related in structure to salicylic acid. They discovered an even more potent compound, which they named ibuprofen, and soon thereafter, Syntex Corporation in the United States developed naproxen and Rhone–Poulenc in France developed ketoprofen:



(*S*)-Ibuprofen



(*S*)-Naproxen



(*S*)-Ketoprofen

Notice that each compound has one stereocenter and can exist as a pair of enantiomers. For each drug, the physiologically active form is the *S* enantiomer. Even though the *R* enantiomer of ibuprofen has none of the analgesic or anti-inflammatory activity, it is converted in the body to the active *S* enantiomer.

In the 1960s, scientists discovered that aspirin acts by inhibiting cyclooxygenase (COX), a key enzyme in the conversion of arachidonic acid to prostaglandins (Section 19.5). With this discovery, it became clear why only one enantiomer of ibuprofen, naproxen, and ketoprofen is active: Only the *S* enantiomer of each has the correct handedness to bind to COX and inhibit its activity.

The discovery that these drugs owe their effectiveness to the inhibition of COX opened an entirely new avenue for drug research. If we know more about the structure and function of this key enzyme, might it be possible to design and discover even more effective nonsteroidal anti-inflammatory drugs for the treatment of rheumatoid arthritis and other inflammatory diseases?

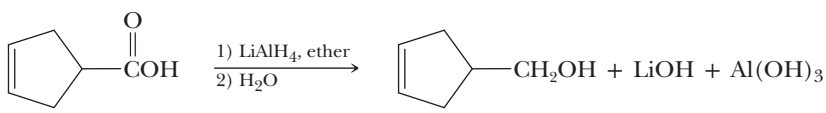
And so continues the story that began with the discovery of the beneficial effects of chewing willow bark.

Question

Draw the product of the reaction of salicylic acid with (a) one equivalent of NaOH, (b) two equivalents of NaOH, (c) two equivalents of $NaHCO_3$.

A. Reduction of a Carboxyl Group

Lithium aluminum hydride, $LiAlH_4$, reduces a carboxyl group to a primary alcohol in excellent yield. Reduction is most commonly carried out in diethyl ether or tetrahydrofuran (THF). The initial product is an aluminum alkoxide, which is then treated with water to give the primary alcohol and lithium and aluminum hydroxides:



3-Cyclopentenecarboxylic acid

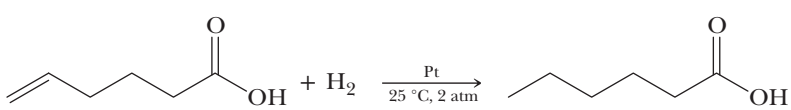
4-Hydroxymethylcyclopentene

These hydroxides are insoluble in diethyl ether or THF and are removed by filtration. Evaporation of the solvent yields the primary alcohol.

Alkenes are generally not affected by metal hydride-reducing reagents. These reagents function as hydride ion donors; that is, they function as nucleophiles, and alkenes are not normally attacked by nucleophiles.

B. Selective Reduction of Other Functional Groups

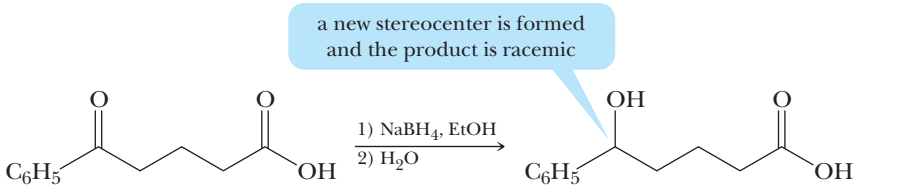
Catalytic hydrogenation (at least under the same conditions used to reduce ketones and aldehydes) does not reduce carboxyl groups, but does reduce alkenes to alkanes. Therefore, we can use H_2/M to reduce this functional group selectively in the presence of a carboxyl group:



5-Hexenoic acid

Hexanoic acid

We saw in Section 12.10 that aldehydes and ketones are reduced to alcohols by both $LiAlH_4$ and $NaBH_4$. Only $LiAlH_4$, however, reduces carboxyl groups. Thus, it is possible to reduce an aldehyde or a ketone carbonyl group selectively in the presence of a carboxyl group by using the less reactive $NaBH_4$ as the reducing agent:



5-Oxo-5-phenylpentanoic acid — 5-Hydroxy-5-phenylpentanoic acid

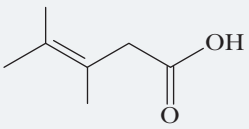
EXAMPLE 13.4

Provide the product formed when each of the following is treated with:

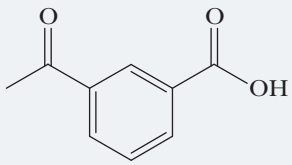
(i) H_2/Pd **(ii)** 1. $LiAlH_4$, ether 2. H_2O **(iii)** 1. $NaBH_4$, EtOH 2. H_2O

In each reaction, assume an excess of reagent is available for reaction.

(a)



(b)



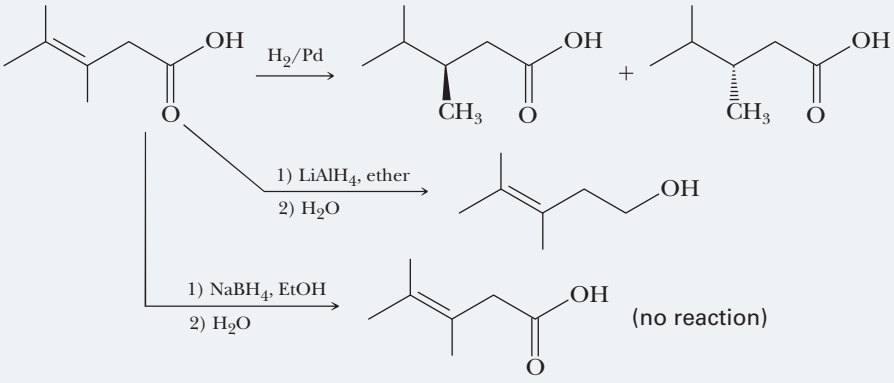
STRATEGY

Remember that carboxyl groups are only reduced by $LiAlH_4$, alkenes are only reduced by H_2/M, aldehydes and ketones are reduced by all metal hydride reducing agents and H_2/M, and benzene rings are resistant to each of these reducing reagents. Remember to consider stereochemistry in the outcome of each reaction.

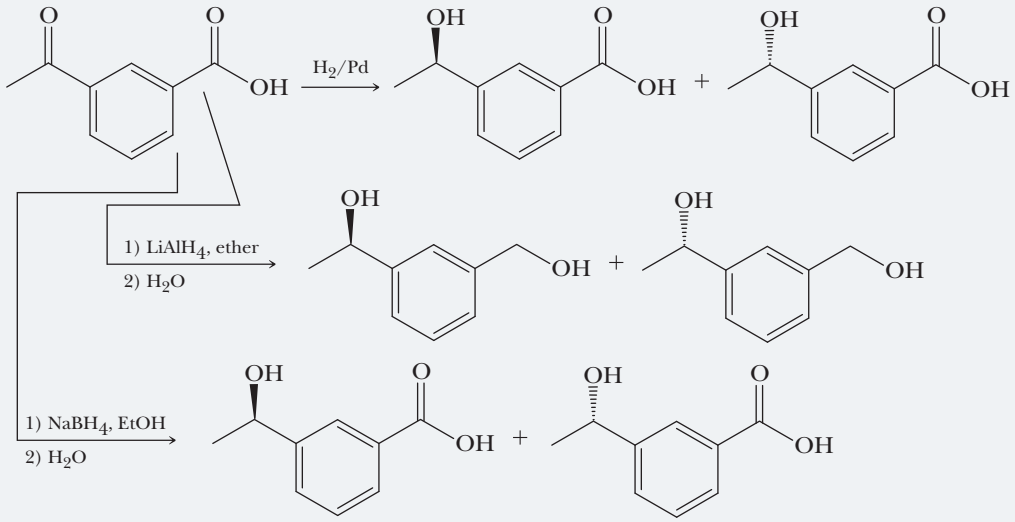
SOLUTION

Here are structural formulas for the major product produced in each reaction:

(a)



(b)



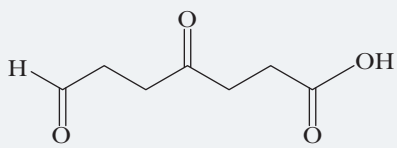
See problems 13.30–13.32, 13.47

PROBLEM 13.4

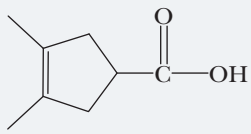
Provide the product formed when each of the following is treated with:
(i) H_2/Pd (ii) 1. $LiAlH_4$, ether 2. H_2O (iii) 1. $NaBH_4$, EtOH 2. H_2O

Presume that an excess of reagent is available for each reaction.

(a)



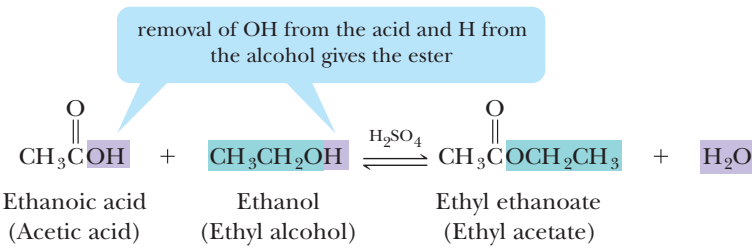
(b)



13.6 What Is Fischer Esterification?

Treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst—most commonly, concentrated sulfuric acid—gives an ester. This method of forming an ester is given the special name **Fischer esterification** after the German chemist Emil Fischer (1852–1919). As an example of Fischer esterification, treating acetic acid with ethanol in the presence of concentrated sulfuric acid gives ethyl acetate and water:

Fischer esterification The process of forming an ester by refluxing a carboxylic acid and an alcohol in the presence of an acid catalyst, commonly sulfuric acid.



Ken Karp for John Wiley & Sons

These products all contain ethyl acetate as a solvent.

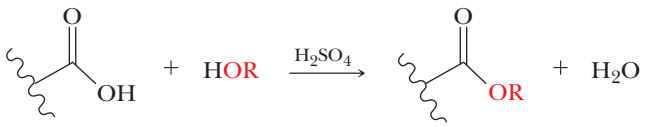
We study the structure, nomenclature, and reactions of esters in detail in Chapter 14. In the present chapter, we discuss only their preparation from carboxylic acids.

Acid-catalyzed esterification is reversible, and generally, at equilibrium, the quantities of remaining carboxylic acid and alcohol are appreciable. By controlling the experimental conditions, however, we can use Fischer esterification to prepare esters in high yields. If the alcohol

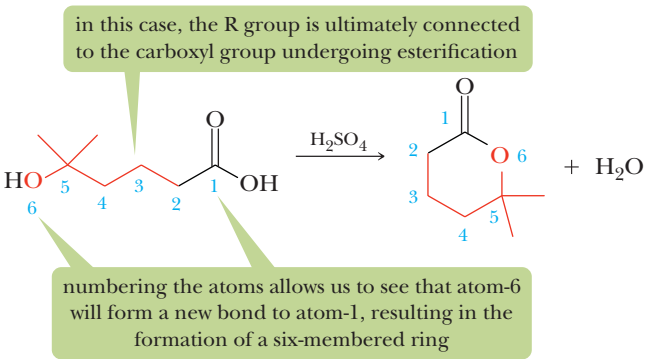
is inexpensive compared with the carboxylic acid, we can use a large excess of the alcohol to drive the equilibrium to the right and achieve a high conversion of carboxylic acid to its ester.

HOW TO 13.1 Predict the Product of a Fischer Esterification

(a) In the Fischer esterification, the —OR portion of an alcohol replaces the —OH portion of a carboxylic acid.

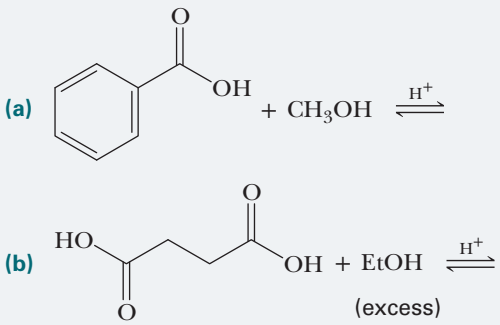


(b) This simple fact of the mechanism allows us to predict the product of any type of Fischer esterification. For example, in the following Fischer esterification, the alcohol is already a part of the molecule. In cases of intramolecular Fischer esterifications, it is often helpful to number the atoms in the molecule.



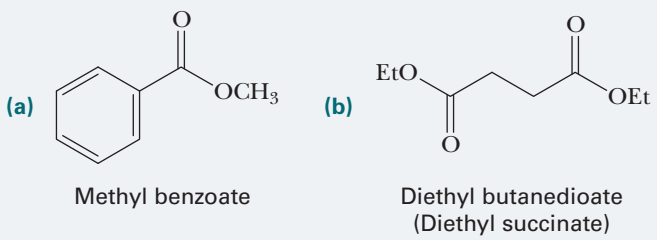
EXAMPLE 13.5

Complete these Fischer esterification reactions:



SOLUTION

Here is a structural formula for the ester produced in each reaction:



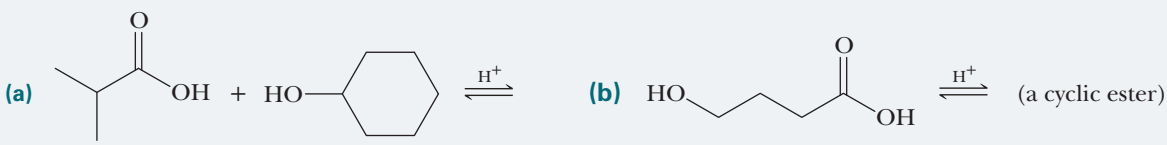
STRATEGY

In a Fischer esterification, each carboxyl group is converted to an ester in which the —OR group originates from the alcohol reagent.

See problems 13.30, 13.33, 13.39, 13.40, 13.47

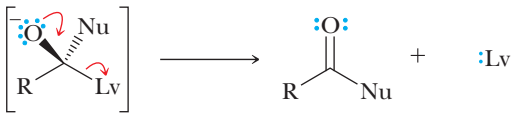
PROBLEM 13.5

Complete these Fischer esterification reactions:



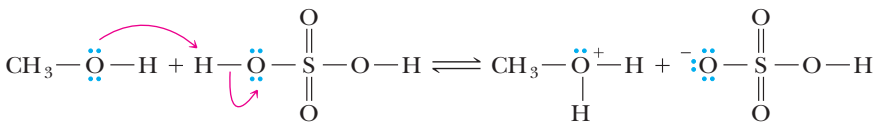
In Section 5.2C, we defined five common mechanistic patterns that we have subsequently seen in a variety of organic reactions. It is now time to define a sixth mechanistic pattern, one that we will encounter often in our study of carboxylic acids and functional derivatives of carboxylic acids (Chapter 14).

Pattern 6: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group. After addition of a nucleophile (Nu:) to a carbonyl, one possible mechanism is for the tetrahedral carbonyl intermediate to collapse back to a C═O while ejecting a leaving group (:Lv). We will see, in this and the chapters to come, that both Nu and Lv can take many forms.



Tetrahedral carbonyl addition intermediate

Following is a mechanism for Fischer esterification, and we urge you to study it carefully. It is important that you understand this mechanism thoroughly because it is a model for many of the reactions of the functional derivatives of carboxylic acids presented in Chapter 14. Note that, although we show the acid catalyst as H_2SO_4 when we write Fisher esterification reactions, the actual proton-transfer acid that initiates the reaction is the oxonium formed by the transfer of a proton from H_2SO_4 (the stronger acid) to the alcohol (the stronger base) used in the esterification reaction:



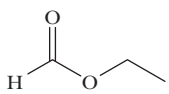
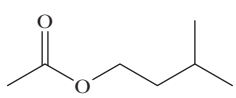
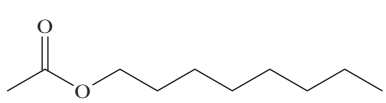
Chemical Connections 13B

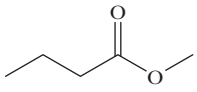
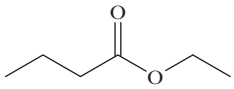
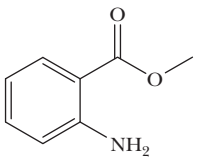
ESTERS AS FLAVORING AGENTS

Flavoring agents are the largest class of food additives. At present, over a thousand synthetic and natural flavors are available. The majority of these are concentrates or extracts from the material whose flavor is desired and are often complex mixtures of from tens to hundreds of compounds. A number of ester flavoring agents are synthesized industrially. The table shows the structures of a few of the esters used as flavoring agents. Many have flavors very close to the target flavor, and adding only one or a few of them is sufficient to make ice cream, soft drinks, or candy taste natural (Isopentane is the common name for 2-methylbutane).

Question

Show how each of the esters in the table can be synthesized using a Fischer esterification reaction.

Structure	Name	Flavor
	Ethyl formate	Rum
	Isopentyl acetate	Banana
	Octyl acetate	Orange

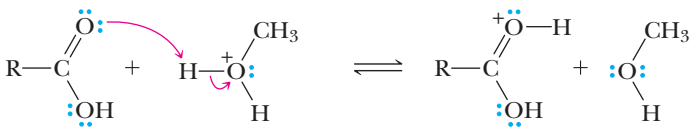
Structure	Name	Flavor
	Methyl butanoate	Apple
	Ethyl butanoate	Pineapple
	Methyl 2-aminobenzoate (Methyl anthranilate)	Grape

Mechanism

Fischer Esterification

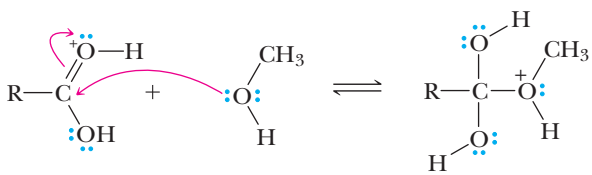
STEP 1: *Add a proton.*

Proton transfer from the acid catalyst to the carbonyl oxygen increases the electrophilicity of the carbonyl carbon:



STEP 2: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*

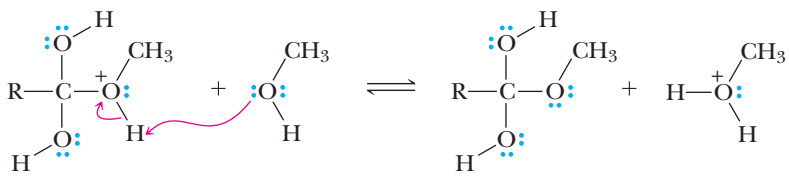
The carbonyl carbon is then attacked by the nucleophilic oxygen atom of the alcohol to form an oxonium ion:



(an electrophile) (a nucleophile) (oxonium ion)

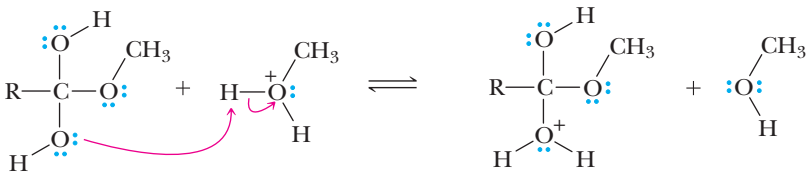
STEP 3: *Take a proton away.*

Proton transfer from the oxonium ion to a second molecule of alcohol gives a tetrahedral carbonyl addition intermediate (TCAI):

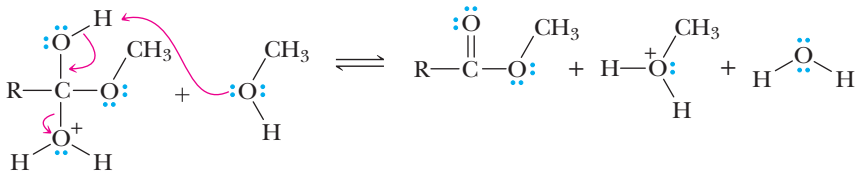


STEP 4: *Add a proton.*

Proton transfer to one of the —OH groups of the TCAI gives a new oxonium ion:

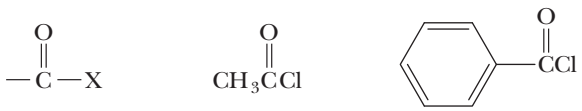


STEP 5: *Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group.*
Loss of water from this oxonium ion gives the ester and regenerates the acid catalyst:



13.7 What Are Acid Chlorides?

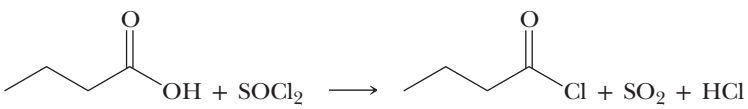
The functional group of an acid halide is a carbonyl group bonded to a halogen atom. Among the acid halides, acid chlorides are the most frequently used in the laboratory and in industrial organic chemistry:



Functional group of an acid halide | Acetyl chloride | Benzoyl chloride

We study the nomenclature, structure, and characteristic reactions of acid halides in Chapter 14. In this chapter, our concern is only with their synthesis from carboxylic acids.

The most common way to prepare an acid chloride is to treat a carboxylic acid with thionyl chloride, the same reagent that converts an alcohol to a chloroalkane (Section 8.2D):



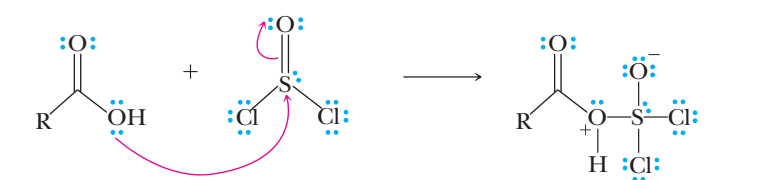
Butanoic acid | Thionyl chloride | Butanoyl chloride

The mechanism of this reaction consists of four steps.

Mechanism

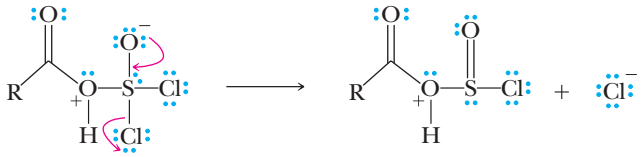
Acid Chloride Formation Using Thionyl Chloride

STEP 1: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
The —OH of the carboxyl group adds to the sulfur atom of thionyl chloride to generate a tetrahedral sulfur intermediate.

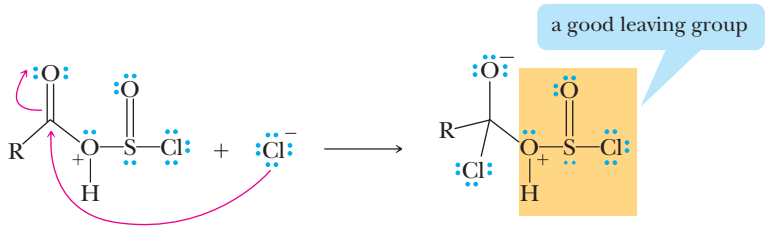


(a nucleophile) (an electrophile) (tetrahedral sulfur intermediate)

STEP 2: *Collapse of the tetrahedral sulfur intermediate to eject a leaving group and regenerate the carbonyl group.*
Loss of chloride from the tetrahedral sulfur intermediate regenerates the sulfonyl group:

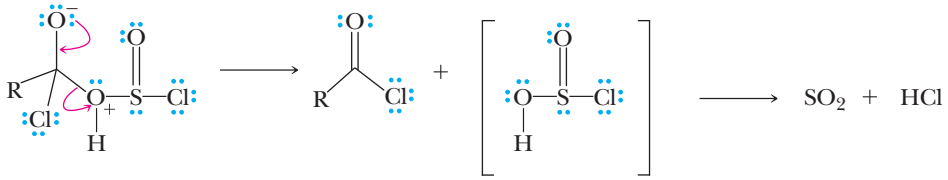


STEP 3: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
The chloride ion attacks the carbonyl carbon, forming a tetrahedral carbonyl addition intermediate.



Tetrahedral carbonyl addition intermediate

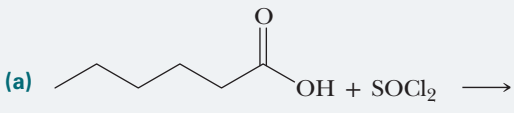
STEP 4: *Collapse of the tetrahedral carbonyl intermediate to eject a leaving group and regenerate the carbonyl group.*
The sulfonyl group highlighted in Step 3 is an excellent leaving group. This allows a lone pair of electrons to collapse back toward the bond to regenerate the carbonyl carbon while expelling the leaving group sulfochloridous acid. This sulfur-based acid is unstable and breaks down to yield sulfur dioxide and HCl. The collapse of a TCAI to regenerate a carbonyl group is a common mode of reactivity for functional derivatives of carboxylic acids (Chapter 14).

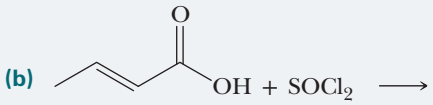


Sulfochloridous acid

EXAMPLE 13.6

Complete each equation:



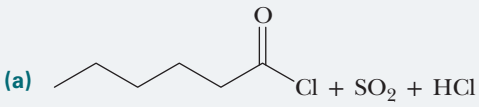


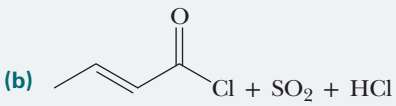
STRATEGY

Thionyl chloride effectively causes —OH groups (for example, those of alcohols and carboxylic acids) to be replaced by Cl. Don't forget to show the by-products of the reaction (SO_2 and HCl).

SOLUTION

Following are the products for each reaction:

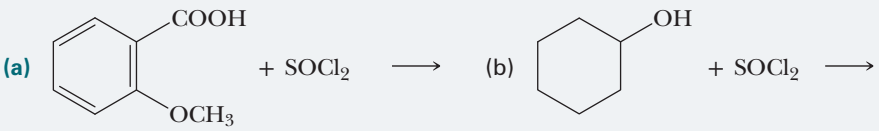




See problems 13.30, 13.47

PROBLEM 13.6

Complete each equation:

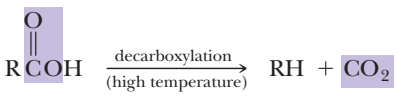


13.8 What Is Decarboxylation?

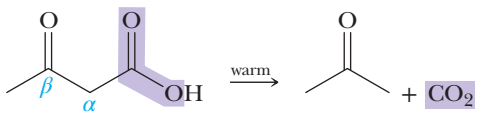
A. β-Ketoacids

Decarboxylation is the loss of CO_2 from a carboxyl group. Almost any carboxylic acid, heated to a very high temperature, undergoes decarboxylation:

Decarboxylation Loss of CO_2 from a carboxyl group.



Most carboxylic acids, however, are quite resistant to moderate heat and melt or even boil without decarboxylation. Exceptions are carboxylic acids that have a carbonyl group β to the carboxyl group. This type of carboxylic acid undergoes decarboxylation quite readily on mild heating. For example, when 3-oxobutanoic acid (acetoacetic acid) is heated moderately, it undergoes decarboxylation to give acetone and carbon dioxide:



3-Oxobutanoic acid (Acetoacetic acid) — Acetone

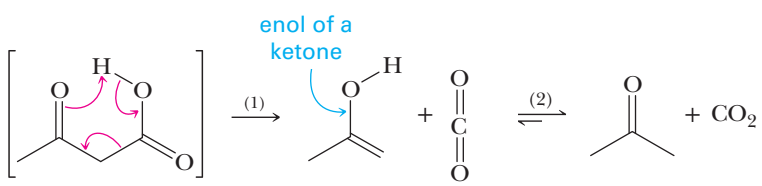
Decarboxylation on moderate heating is a unique property of 3-oxocarboxylic acids (β-ketoacids) and is not observed with other classes of ketoacids.

Mechanism

Decarboxylation of a β-Ketocarboxylic Acid

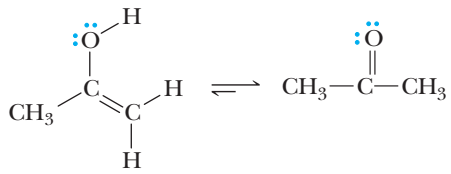
STEP 1: *Rearrangement of bonds.*

Redistribution of six electrons in a cyclic six-membered transition state gives carbon dioxide and an enol:



(A cyclic six-membered transition state)

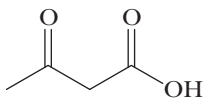
STEP 2: *Keto–enol tautomerism.*
Tautomerism (Section 12.8A) of the enol gives the more stable keto form of the product:



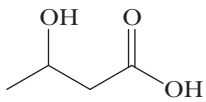
Chemical Connections 13C

KETONE BODIES AND DIABETES

3-Oxobutanoic acid (acetoacetic acid) and its reduction product, 3-hydroxybutanoic acid, are synthesized in the liver from acetyl-CoA, a product of the metabolism of fatty acids (Section 21.5C) and certain amino acids:



3-Oxobutanoic acid
(Acetoacetic acid)



3-Hydroxybutanoic acid
(β-Hydroxybutyric acid)

3-Hydroxybutanoic acid and 3-oxobutanoic acid are known collectively as ketone bodies.

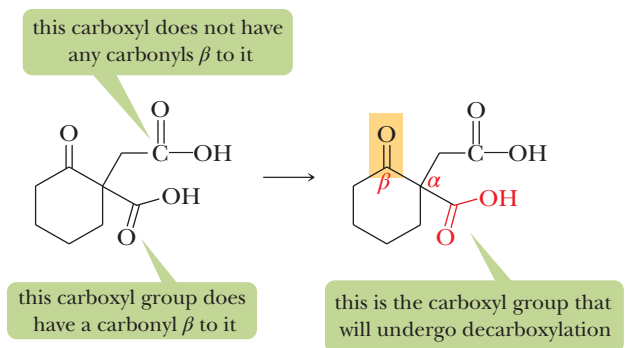
The concentration of ketone bodies in the blood of healthy, well-fed humans is approximately 0.01 mM/L. However, in persons suffering from starvation or diabetes mellitus, the concentration of ketone bodies may increase to as much as 500 times normal. Under these conditions, the concentration of acetoacetic acid increases to the point where it undergoes spontaneous decarboxylation to form acetone and carbon dioxide. Acetone is not metabolized by humans and is excreted through the kidneys and the lungs. The odor of acetone is responsible for the characteristic "sweet smell" on the breath of severely diabetic patients.

Question
Show the mechanism for the decarboxylation of acetoacetic acid. Explain why 3-hydroxybutanoic acid cannot undergo decarboxylation.

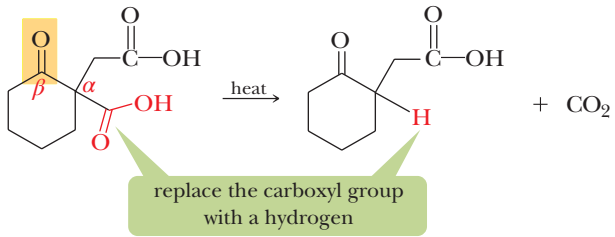
HOW TO 13.2

Predict the Product of a β-Decarboxylation Reaction

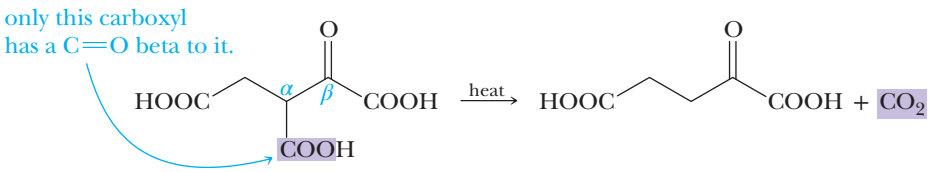
(a) The most important criterion of a decarboxylation reaction is that the carbonyl group be at the β-position relative to a carboxyl group. Therefore, identify each carboxyl group in a molecule and determine whether a carbonyl is β to it.



(b) Once all the carboxyl groups with β-carbonyls are identified, it is a simple matter of replacing the carboxyl groups with a hydrogen.



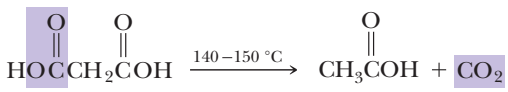
An important example of decarboxylation of a β-ketoacid in the biological world occurs during the oxidation of foodstuffs in the tricarboxylic acid (TCA) cycle. Oxalosuccinic acid, one of the intermediates in this cycle, undergoes spontaneous decarboxylation to produce α-ketoglutaric acid. Only one of the three carboxyl groups of oxalosuccinic acid has a carbonyl group in the position β to it, and it is this carboxyl group that is lost as CO_2:



Oxalosuccinic acid α-Ketoglutaric acid

B. Malonic Acid and Substituted Malonic Acids

The presence of a ketone or an aldehyde carbonyl group on the carbon β to the carboxyl group is sufficient to facilitate decarboxylation. In the more general reaction, decarboxylation is facilitated by the presence of any carbonyl group on the β carbon, including that of a carboxyl group or an ester. Malonic acid and substituted malonic acids, for example, undergo decarboxylation on heating, as illustrated by the decarboxylation of malonic acid when it is heated slightly above its melting point of 135–137 °C:



Propanedioic acid (Malonic acid)

The mechanism for decarboxylation of malonic acids is similar to what we have just studied for the decarboxylation of β-ketoacids. The formation of a cyclic, six-membered transition state involving a redistribution of three electron pairs gives the enol form of a carboxylic acid, which, in turn, isomerizes to the carboxylic acid.

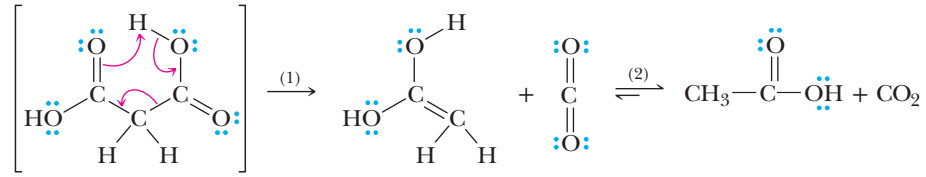
Mechanism

Decarboxylation of a β-Dicarboxylic Acid

STEP 1: *Rearrangement of bonds.*

Rearrangement of six electrons in a cyclic six-membered transition state gives carbon dioxide and the enol form of a carboxyl group.

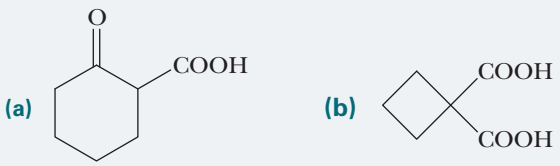
STEP 2: *Keto–enol tautomerism.*
Tautomerism (Section 12.8A) of the enol gives the more stable keto form of the carboxyl group.



A cyclic six-membered transition state | Enol of a carboxyl group

EXAMPLE 13.7

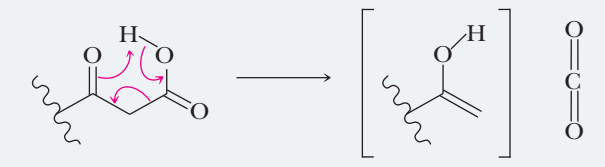
Each of these carboxylic acids undergoes thermal decarboxylation:



Draw a structural formula for the enol intermediate and final product formed in each reaction.

STRATEGY

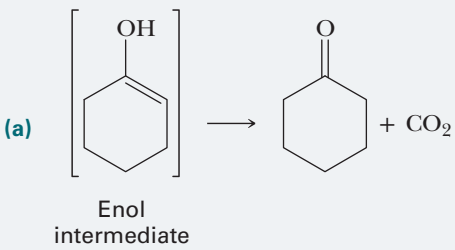
It is often helpful to draw the full Lewis structure of the β-carboxyl group and to position it to allow a cyclic six-membered transition state:



A cyclic six-membered transition state | Enol | CO_2

By carefully keeping track of the movement of electrons, the bonds made and the bonds broken, one can arrive at the enol intermediate. Predicting the final product is a simple matter of replacing the —COOH group that is β to a carbonyl in the molecule with a hydrogen atom.

SOLUTION

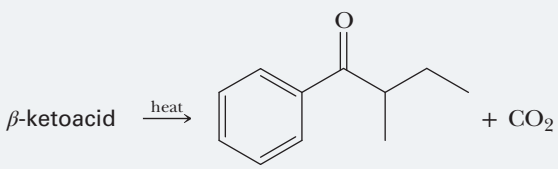


Enol intermediate

See problems 13.41, 13.47

PROBLEM 13.7

Draw the structural formula for the indicated β-ketoacid:



SUMMARY OF KEY QUESTIONS

13.1 What Are Carboxylic Acids?

- The functional group of a **carboxylic acid** is the **carboxyl group,** —**COOH**.

13.2 How Are Carboxylic Acids Named?

- IUPAC names of carboxylic acids are derived from the parent alkane by dropping the suffix *-e* and adding *-oic acid*.
- Dicarboxylic acids are named as *-dioic acids*.

13.3 What Are the Physical Properties of Carboxylic Acids?

- Carboxylic acids are polar compounds that associate by hydrogen bonding into **dimers** in the liquid and solid states.
- Carboxylic acids have higher boiling points and are more soluble in water than alcohols, aldehydes, ketones, and ethers of comparable molecular weight.
- A carboxylic acid consists of two regions of different polarity: a polar, **hydrophilic** carboxyl group, which increases solubility in water, and a nonpolar, **hydrophobic** hydrocarbon chain, which decreases solubility in water.
- The first four **aliphatic carboxylic acids** are infinitely soluble in water because the hydrophilic carboxyl group more than counterbalances the hydrophobic hydrocarbon chain.
- As the size of the carbon chain increases, the hydrophobic group becomes dominant, and solubility in water decreases.

13.4 What Are the Acid–Base Properties of Carboxylic Acids?

- Values of pK_a for aliphatic carboxylic acids are in the 4.0 to 5.0 range.
- Electron-withdrawing substituents near the carboxyl group increase acidity in both aliphatic and aromatic carboxylic acids.

13.5 How Are Carboxyl Groups Reduced?

- The carboxyl group is one of the organic functional groups that is most resistant to reduction. They do not react with H_2/M or $NaBH_4$.
- Lithium aluminum hydride, $LiAlH_4$, reduces a carboxyl group to a primary alcohol.

13.6 What Is Fischer Esterification?

- **Fischer esterification** is a method of forming an ester by treatment of a carboxylic acid with an alcohol in the presence of an acid catalyst.

13.7 What Are Acid Chlorides?

- The functional group of an **acid chloride** is a carbonyl group bonded to a chlorine atom.
- The most common way to prepare an acid chloride is to treat a carboxylic acid with **thionyl chloride**.

13.8 What Is Decarboxylation?

- **Decarboxylation** is the loss of CO_2 from a carboxyl group.
- Carboxylic acids that have a carbonyl group β to the carboxyl group readily undergo decarboxylation on mild heating.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. In naming carboxylic acids, it is always necessary to indicate the position at which the carboxyl group occurs. (13.2)
2. 2-Propylpropanedioic acid can undergo decarboxylation at relatively moderate temperatures. (13.8)
3. Fischer esterification is reversible. (13.6)
4. The hydrophilic group of a carboxylic acid decreases water solubility. (13.3)
5. Both alcohols and carboxylic acids react with $SOCl_2$. (13.7)
6. Fischer esterification involves the reaction of a carboxylic acid with another carboxylic acid. (13.6)
7. An electronegative atom on a carboxylic acid can potentially increase the acid's acidity. (13.4)
8. A carboxyl group is reduced to a 1° alcohol by H_2/Pt. (13.5)
9. A carboxyl group is reduced to a 1° alcohol by $NaBH_4$. (13.5)
10. A carboxyl group that has been deprotonated is called a carboxylate group. (13.4)
11. A carboxyl group is reduced to a 1° alcohol by $LiAlH_4$. (13.5)
12. The conjugate base of a carboxylic acid is resonance-stabilized. (13.4)

13. Carboxylic acids possess both a region of polarity and a region of nonpolarity. (13.3)

14. Carboxylic acids are less acidic than phenols. (13.4)

15. 4-Oxopentanoic acid can undergo decarboxylation at relatively moderate temperatures. (13.8)

16. The γ position of a carboxylic acid refers to carbon-4 of the chain. (13.2)

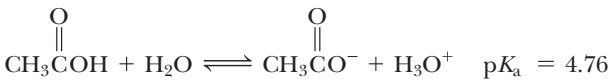
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) F (2) T (3) T (4) F (5) T (6) F (7) T (8) F (9) F (10) T (11) T (12) T (13) T (14) F (15) F (16) T

KEY REACTIONS

1. Acidity of Carboxylic Acids (Section 13.4A)

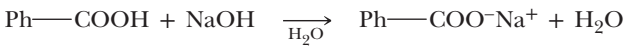
Values of pK_a for most unsubstituted aliphatic and aromatic carboxylic acids are within the range from 4 to 5:



Substitution by electron-withdrawing groups decreases pK_a (increases acidity).

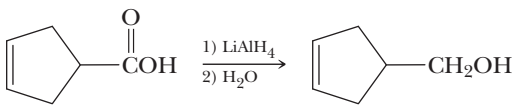
2. Reaction of Carboxylic Acids with Bases (Section 13.4B)

Carboxylic acids form water-soluble salts with alkali metal hydroxides, carbonates, and bicarbonates, as well as with ammonia and amines:



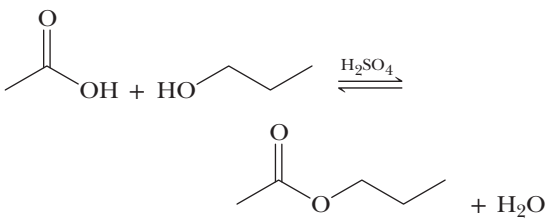
3. Reduction by Lithium Aluminum Hydride (Section 13.5)

Lithium aluminum hydride reduces a carboxyl group to a primary alcohol:



4. Fischer Esterification (Section 13.6)

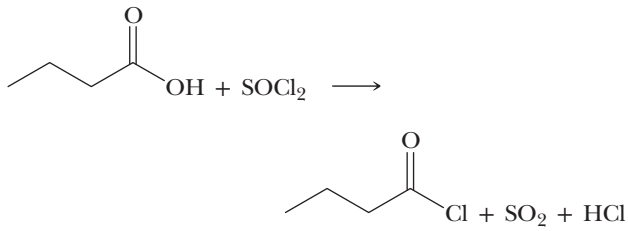
Fischer esterification is reversible:



One way to force the equilibrium to the right is to use an excess of the alcohol.

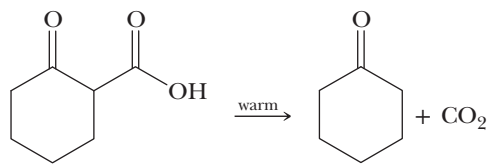
5. Conversion to Acid Halides (Section 13.7)

Acid chlorides, the most common and widely used of the acid halides, are prepared by treating carboxylic acids with thionyl chloride:



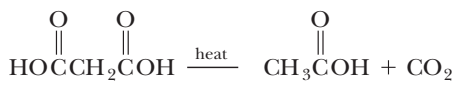
6. Decarboxylation of β-Ketoacids (Section 13.8A)

The mechanism of decarboxylation involves the redistribution of bonding electrons in a cyclic, six-membered transition state:



7. Decarboxylation of β-Dicarboxylic Acids (Section 13.8B)

The mechanism of decarboxylation of a β-dicarboxylic acid is similar to that for decarboxylation of a β-ketoacid:



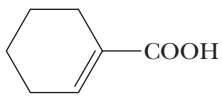
PROBLEMS

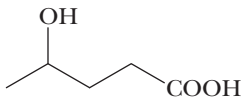
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

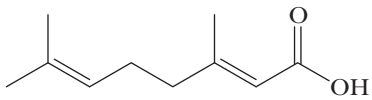
SECTION 13.2 Structure and Nomenclature

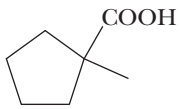
13.8 Name and draw structural formulas for the four carboxylic acids with the molecular formula $C_5H_{10}O_2$. Which of these carboxylic acids is chiral?

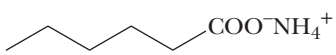
13.9 Write the IUPAC name for each compound: **(See Example 13.1)**

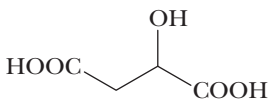
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

13.10 Draw a structural formula for each carboxylic acid: **(See Example 13.1)**

(a) 4-Nitrophenylacetic acid
(b) 4-Aminopentanoic acid
(c) 3-Chloro-4-phenylbutanoic acid
(d) *cis*-3-Hexenedioic acid
(e) 2,3-Dihydroxypropanoic acid
(f) 3-Oxohexanoic acid
(g) 2-Oxocyclohexanecarboxylic acid
(h) 2,2-Dimethylpropanoic acid

***13.11** Megatomoic acid, the sex attractant of the female black carpet beetle, has the structure **(See Example 13.1)**

$$CH_3(CH_2)_7CH{=}CHCH{=}CHCH_2COOH$$

Megatomoic acid

(a) What is the IUPAC name of megatomoic acid?
(b) State the number of stereoisomers possible for this compound.

***13.12** The IUPAC name of ibuprofen is 2-(4-isobutylphenyl) propanoic acid. Draw a structural formula of ibuprofen. **(See Example 13.1)**

***13.13** Draw structural formulas for these salts:

(a) Sodium benzoate
(b) Lithium acetate
(c) Ammonium acetate
(d) Disodium adipate
(e) Sodium salicylate
(f) Calcium butanoate

***13.14** The monopotassium salt of oxalic acid is present in certain leafy vegetables, including rhubarb. Both oxalic acid and its salts are poisonous in high concentrations. Draw a structural formula of monopotassium oxalate.

***13.15** Potassium sorbate is added as a preservative to certain foods to prevent bacteria and molds from causing spoilage and to extend the foods' shelf life. The IUPAC name of potassium sorbate is potassium (2*E*,4*E*)-2,4-hexadienoate. Draw a structural formula of potassium sorbate. **(See Example 13.1)**

***13.16** Zinc 10-undecenoate, the zinc salt of 10-undecenoic acid, is used to treat certain fungal infections, particularly *tinea pedis* (athlete's foot). Draw a structural formula of this zinc salt.

SECTION 13.3 Physical Properties

13.17 Arrange the compounds in each set in order of increasing boiling point:

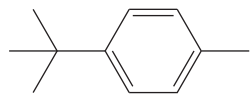
(a) $CH_3(CH_2)_5COOH$ $CH_3(CH_2)_6CHO$ $CH_3(CH_2)_6CH_2OH$

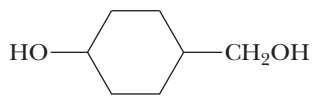
(b) CH_3CH_2COOH $CH_3CH_2CH_2CH_2OH$ $CH_3CH_2OCH_2CH_3$

SECTION 13.4 Preparation of Carboxylic Acids

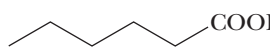
13.18 Draw a structural formula for the product formed by treating each compound with warm chromic acid, H_2CrO_4:

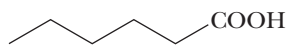
(a) $CH_3(CH_2)_4CH_2OH$

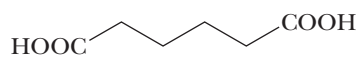
(b) 

(c) 

13.19 Draw a structural formula for a compound with the given molecular formula that, on oxidation by chromic acid, gives the carboxylic acid or dicarboxylic acid shown:

(a) $C_6H_{14}O \xrightarrow{\text{oxidation}}$ 

(b) $C_6H_{12}O \xrightarrow{\text{oxidation}}$ 

(c) $C_6H_{14}O_2 \xrightarrow{\text{oxidation}}$ 

Acidity of Carboxylic Acids

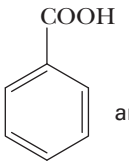
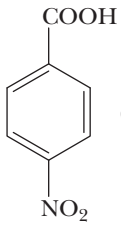
13.20 Which is the stronger acid in each pair? **(See Example 13.2)**

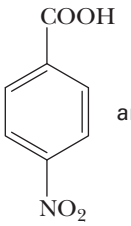
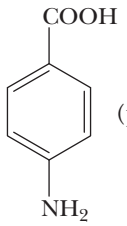
(a) Phenol (pK_a 9.95) or benzoic acid (pK_a 4.17)

(b) Lactic acid (K_a 1.4×10^{-4}) or ascorbic acid (K_a 6.8×10^{-5})

13.21 Arrange these compounds in order of increasing acidity: benzoic acid, benzyl alcohol, and phenol. **(See Example 13.2)**

13.22 Assign the acid in each set its appropriate pK_a **(See Example 13.2)**

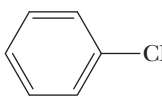
(a)  and  (pK_a 4.19 and 3.14)

(b)  and  (pK_a 4.92 and 3.14)

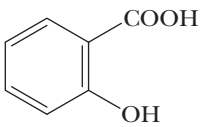
(c) CH_3CCH_2COOH and CH_3CCOOH (pK_a 3.58 and 2.49)

(d) $CH_3CHCOOH$ and CH_3CH_2COOH (pK_a 3.85 and 4.78)

13.23 Complete these acid–base reactions: **(See Example 13.3)**

(a)  $+ NaOH \longrightarrow$

(b) $CH_3CH{=}CHCH_2COOH + NaHCO_3 \longrightarrow$

(c)  $+ NaHCO_3 \longrightarrow$

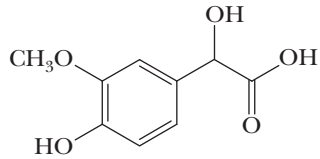
(d) $CH_3CHCOOH + H_2NCH_2CH_2OH \longrightarrow$

(e) $CH_3CH{=}CHCH_2COO^-Na^+ + HCl \longrightarrow$

***13.24** The normal pH range for blood plasma is 7.35–7.45. Under these conditions, would you expect the carboxyl group of lactic acid (pK_a 3.85) to exist primarily as a carboxyl group or as a carboxylate anion? Explain.

***13.25** The pK_a of salicylic acid (Section 13.2), is 2.97. Would you expect salicylic acid dissolved in blood plasma (pH 7.35–7.45) to exist primarily as salicylic acid or as salicylate anion? Explain.

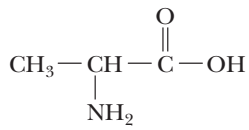
***13.26** Vanillylmandelic acid (pK_a 3.42) is a metabolite found in urine, the pH of which is normally in the range from 4.8 to 8.4. Provide the structure of vanillylmandelic acid that you would expect to find in urine with pH 5.8?



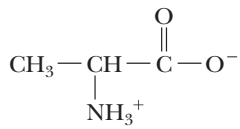
Vanillylmandelic acid

***13.27** The pH of human gastric juice is normally in the range from 1.0 to 3.0. What form of lactic acid (pK_a 3.85), lactic acid itself or its anion, would you expect to be present in the stomach?

***13.28** Following are two structural formulas for the amino acid alanine (Section 18.2):



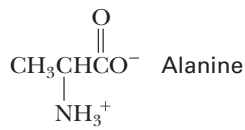
(A)



(B)

Is alanine better represented by structural formula A or B? Explain.

13.29 In Chapter 18, we discuss a class of compounds called amino acids, so named because they contain both an amino group and a carboxyl group. Following is a structural formula for the amino acid alanine in the form of an internal salt:

 Alanine

What would you expect to be the major form of alanine present in aqueous solution at (a) pH 2.0, (b) pH 5–6, and (c) pH 11.0? Explain.

SECTIONS 13.5–13.8 Reactions of Carboxylic Acids

13.30 Give the expected organic products formed when phenylacetic acid, $PhCH_2COOH$, is treated with each of the following reagents: **(See Examples 13.4–13.6)**

(a) $SOCl_2$

(b) $NaHCO_3$, H_2O

(c) $NaOH$, H_2O

(d) NH_3, H_2O

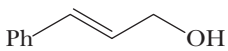
(e) $LiAlH_4$, followed by H_2O

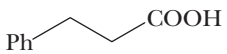
(f) $NaBH_4$, followed by H_2O

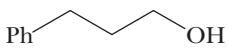
(g) $CH_3OH + H_2SO_4$ (catalyst)

(h) H_2/Ni at 25 °C and 3 atm pressure

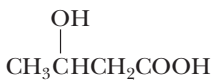
13.31 Show how to convert *trans*-3-phenyl-2-propenoic acid (cinnamic acid) to these compounds: **(See Example 13.4)**

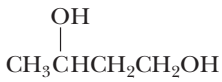
(a) 

(b) 

(c) 

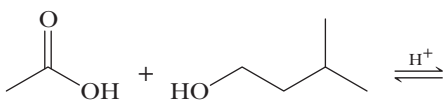
13.32 Show how to convert 3-oxobutanoic acid (acetoacetic acid) to these compounds: **(See Example 13.4)**

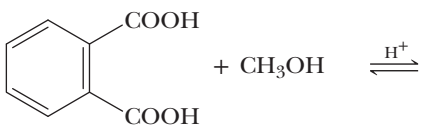
(a) 

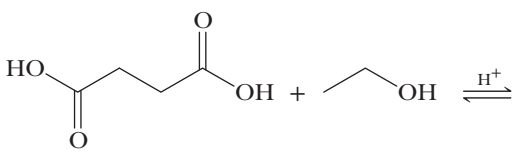
(b) 

(c) $CH_3CH{=}CHCOOH$

13.33 Complete these examples of Fischer esterification (assume an excess of the alcohol): **(See Example 13.5)**

(a) 

(b) 

(c) 

***13.34** Formic acid is one of the components responsible for the sting of biting ants and is injected under the skin by bees and wasps. A way to relieve the pain is to rub the area of the sting with a paste of baking soda ($NaHCO_3$) and water, which neutralizes the acid. Write an equation for this reaction. **(See Example 13.3)**

***13.35** Methyl 2-hydroxybenzoate (methyl salicylate) has the odor of oil of wintergreen. This ester is prepared by the Fischer esterification of 2-hydroxybenzoic acid (salicylic acid) with methanol. Draw a structural formula of methyl 2-hydroxybenzoate.

***13.36** Benzocaine, a topical anesthetic, is prepared by treating 4-aminobenzoic acid with ethanol in the presence of an acid catalyst, followed by neutralization. Draw a structural formula of benzocaine.

***13.37** Examine the structural formulas of pyrethrin and permethrin. (See Chemical Connections 14D.)

(a) Locate the ester groups in each compound.

(b) Is pyrethrin chiral? How many stereoisomers are possible for it?

(c) Is permethrin chiral? How many stereoisomers are possible for it?

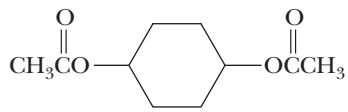
***13.38** A commercial Clothing & Gear Insect Repellant gives the following information about permethrin, its active ingredient:

Cis/trans ratio: Minimum 35% (+/–) *cis* and maximum 65% (+/–) *trans*

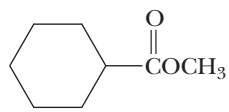
(a) To what does the *cis/trans* ratio refer?

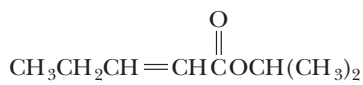
(b) To what does the designation "(+/–)" refer?

13.39 From what carboxylic acid and alcohol is each of the following esters derived? **(See Example 13.5)**

(a) 

(b) 

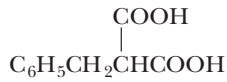
(c) 

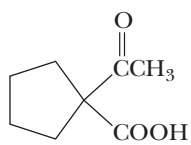
(d) 

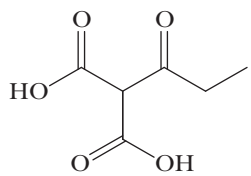
13.40 When treated with an acid catalyst, 4-hydroxybutanoic acid forms a cyclic ester (a lactone). Draw the structural formula of this lactone. **(See Example 13.5)**

13.41 Draw a structural formula for the product formed on thermal decarboxylation of each of the following compounds: **(See Example 13.7)**

(a) 

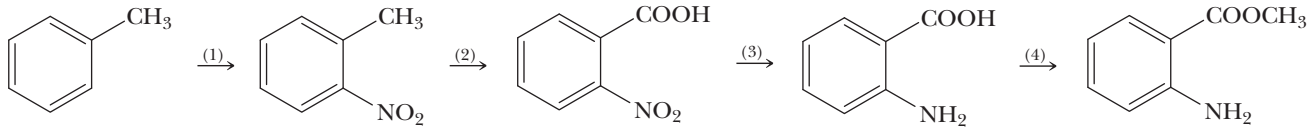
(b) 

(c) 

(d) 

Synthesis

***13.42** Methyl 2-aminobenzoate, a flavoring agent with the taste of grapes (see Chemical Connections 13B), can be prepared from toluene by the following series of steps:

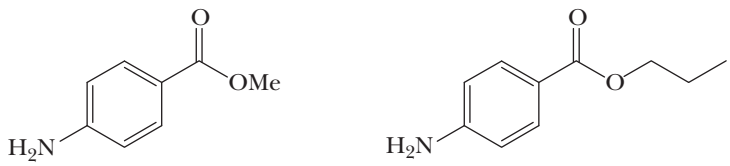


Toluene

Methyl 2-amino-benzoate

Show how you might bring about each step in this synthesis.

***13.43** Methylparaben and propylparaben are used as preservatives in foods, beverages, and cosmetics:

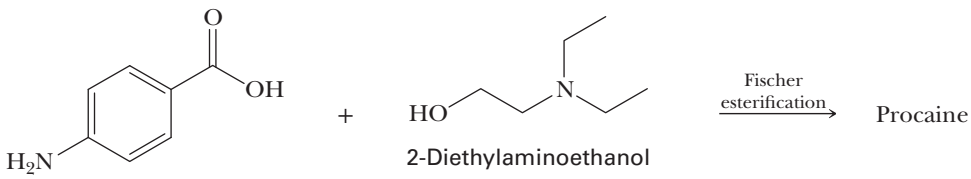


Methyl 4-aminobenzoate (Methylparaben)

Propyl 4-aminobenzoate (Propylparaben)

Show how the synthetic scheme in Problem 13.42 can be modified to give each of these compounds.

***13.44** Procaine (its hydrochloride is marketed as Novocaine®) was one of the first local anesthetics developed for infiltration and regional anesthesia. It is synthesized by the following Fischer esterification:

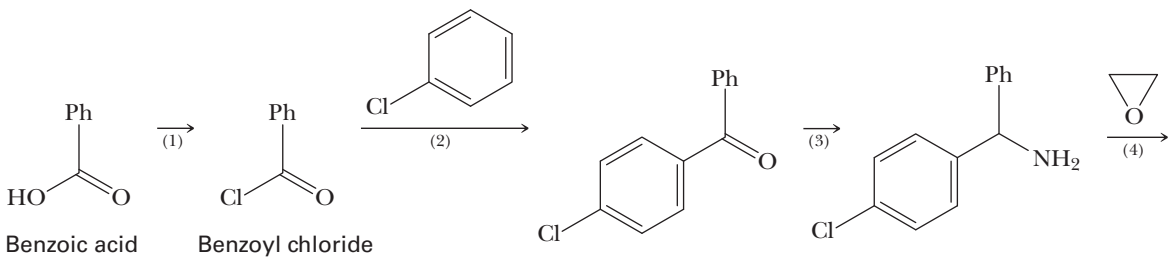


p-Aminobenzoic acid

2-Diethylaminoethanol

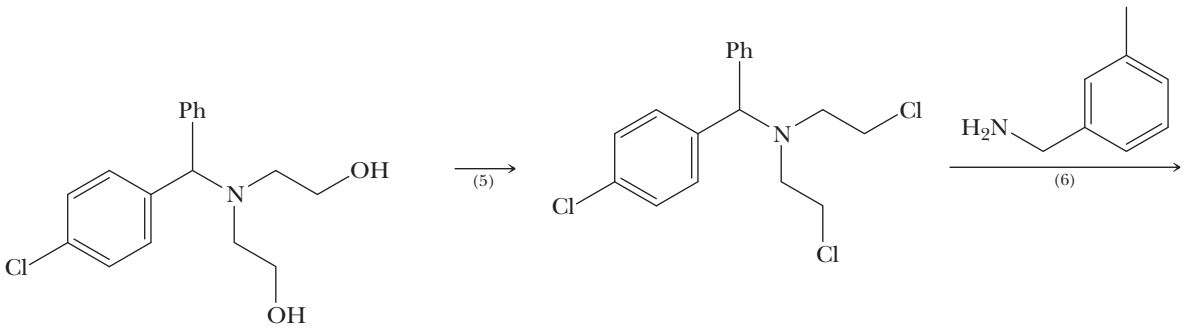
Draw a structural formula for procaine.

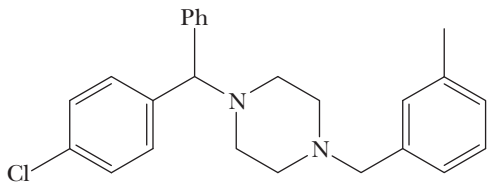
***13.45** Meclizine is an antiemetic: It helps prevent, or at least lessen, the vomiting associated with motion sickness, including seasickness. Among the names of the over-the-counter preparations of meclizine are Bonine®, Sea-Legs, Antivert®, and Navicalm®. Meclizine can be synthesized by the following series of steps:



Benzoic acid

Benzoyl chloride





Meclizine

(a) Propose a reagent for Step 1.

(b) The catalyst for Step 2 is $AlCl_3$ Name the type of reaction that occurs in Step 2.

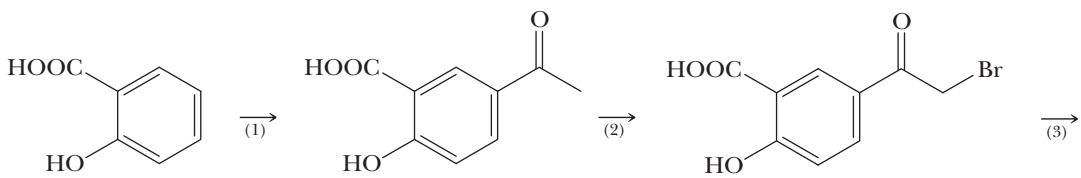
(c) Propose reagents for Step 3.

(d) Propose a mechanism for Step 4, and show that it is an example of nucleophilic aliphatic substitution.

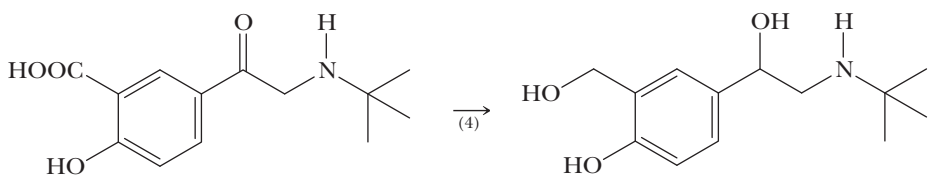
(e) Propose a reagent for Step 5.

(f) Show that Step 6 is also an example of nucleophilic aliphatic substitution.

***13.46** Chemists have developed several syntheses for the antiasthmatic drug albuterol (Proventil). One of these syntheses starts with salicylic acid, the same acid that is the starting material for the synthesis of aspirin:



Salicylic acid



Albuterol

(a) Propose a reagent and a catalyst for Step 1. What name is given to this type of reaction?

(b) Propose a reagent for Step 2.

(c) Name the amine used to bring about Step 3.

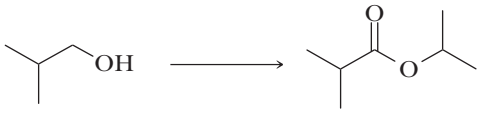
(d) Step 4 is a reduction of two functional groups. Name the functional groups reduced and tell what reagent will accomplish the reduction.

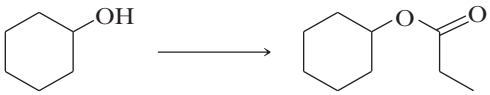
(e) Is albuterol chiral? If so how many stereoisomers are possible?

(f) Would the albuterol formed in this synthesis be optically active or optically inactive? That is, would it be formed as a single enantiomer or as a racemic mixture?

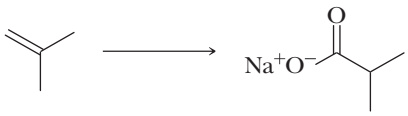
CHEMICAL TRANSFORMATIONS

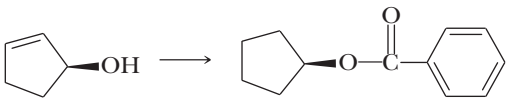
13.47 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note*: Some will require more than one step. **(See Examples 13.4–13.7)**

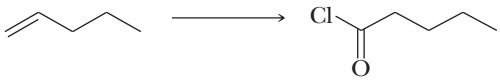
(a) 

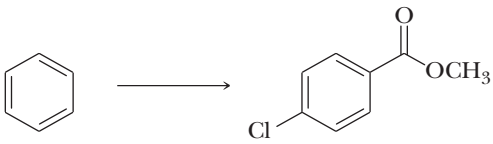
(b) 

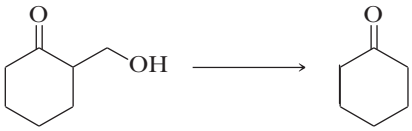
(c) 

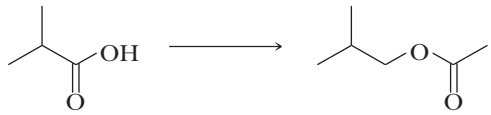
(d) 

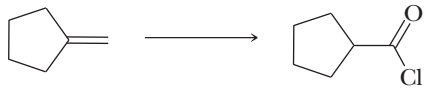
(e) 

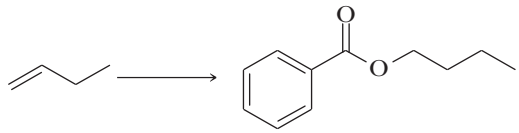
(f) 

(g) 

(h) 

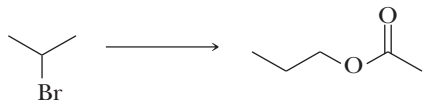
(i) 

(j) 

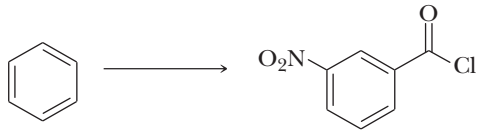
(k) 

(l) 

(m) 

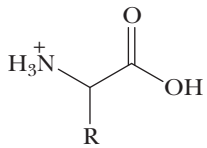
(n) 

(o) 

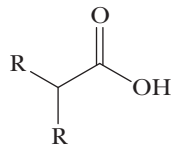
(p) 

LOOKING AHEAD

13.48 Explain why α-amino acids, the building blocks of proteins (Chapter 18), are nearly a thousand times more acidic than aliphatic carboxylic acids: **(See Example 13.2)**



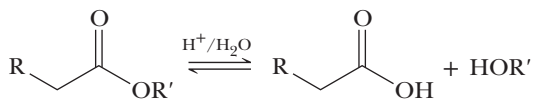
An α-amino acid
$pK_a \approx 2$



An aliphatic acid
$pK_a \approx 5$

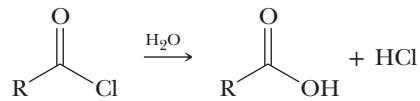
13.49 Which is more difficult to reduce with $LiAlH_4$, a carboxylic acid or a carboxylate ion?

13.50 Show how an ester can react with H^+/H_2O to give a carboxylic acid and an alcohol (*Hint:* This is the reverse of Fischer esterification):



13.51 In Chapter 12, we saw how Grignard reagents readily attack the carbonyl carbon of ketones and aldehydes. Should the same process occur with Grignards and carboxylic acids? With esters?

13.52 In Section 13.6, it was suggested that the mechanism for the Fischer esterification of carboxylic acids would be a model for many of the reactions of the functional derivatives of carboxylic acids. One such reaction, the reaction of an acid halide with water, is the following:



Suggest a mechanism for this reaction.

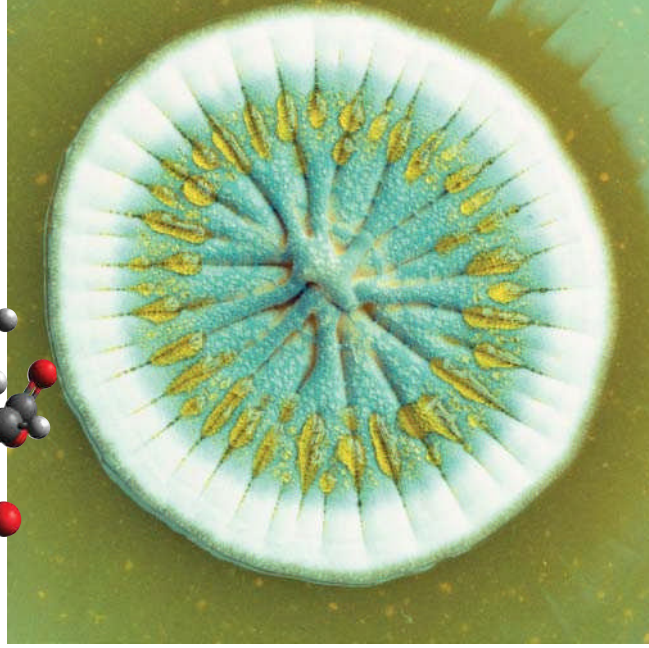
GROUP LEARNING ACTIVITIES

13.53 What acids are more acidic (lower pK_a) than carboxylic acids? What acids are less acidic (higher pK_a) than carboxylic acids? List and discuss any trends in this list of acids.

13.54 We learned that after it is formed by the attack of a nucleophile, the TCAI of a carboxylic acid can collapse to eject a leaving group and regenerate the carbonyl group. Discuss why the TCAIs of ketones and aldehydes don't undergo this same collapse.

Functional Derivatives of Carboxylic Acids

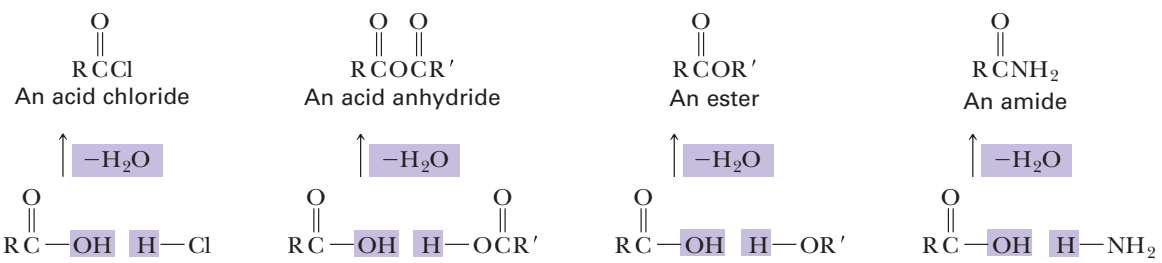
14



Andrew McClenaghan/Photo Researchers, Inc.

Macrophotograph of the fungus *Penicillium notatum* growing on a petri dish culture of Whickerman's agar. This fungus was used as an early source of the first penicillin antibiotic. Inset: A model of penicillin G, a compound that contains two amide functional groups. Amides are functional derivatives of carboxylic acids.

IN THIS CHAPTER, we study four classes of organic compounds, all derived from the carboxyl group (—COOH): acid halides, acid anhydrides, esters, and amides. Under the general formula of each functional group is a drawing to help you see how the group is formally related to a carboxyl group. The loss of —OH from a carboxyl group and H— from H—Cl, for example, gives an acid chloride, and similarly, the loss of —OH from a carboxyl group and H— from ammonia gives an amide:

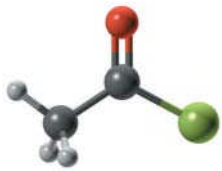


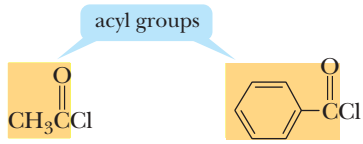
14.1 What Are Some Derivatives of Carboxylic Acids, and How Are They Named?

A. Acid Halides

The functional group of an **acid halide** (acyl halide) is an **acyl group (RCO—)** bonded to a halogen atom (Section 13.7). The most common acid halides are acid chlorides:

Acid halide A derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen—most commonly, chlorine.





Ethanoyl chloride (Acetyl chloride) Benzoyl chloride

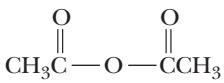
Acid halides are named by changing the suffix *-ic acid* in the name of the parent carboxylic acid to *-yl halide*.

B. Acid Anhydrides

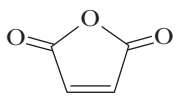
Carboxylic Anhydrides

The functional group of a **carboxylic anhydride** (commonly referred to simply as an anhydride) is two acyl groups bonded to an oxygen atom. The anhydride may be symmetrical (having two identical acyl groups), it may be cyclic, or it may be mixed (having two different acyl groups). Symmetrical anhydrides are named by changing the suffix *acid* in the name of the parent carboxylic acid to *anhydride*.

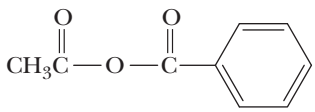
Carboxylic anhydride A compound in which two acyl groups are bonded to an oxygen.



Acetic anhydride

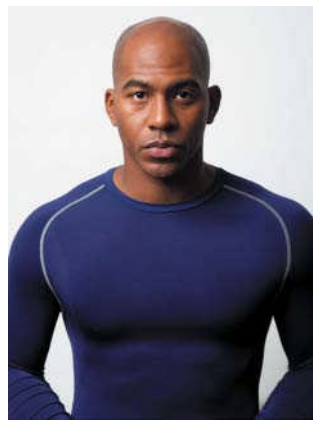


Maleic anhydride



Acetic benzoic anhydride (a mixed anhydride)

Mixed anhydrides are named by identifying the two parent carboxylic acids from both acyl groups and placing those names in succession, in alphabetical order, without the "acid" part of the name followed by the word *anhydride*.

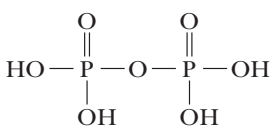


© Image Source/Alamy Stock Photo

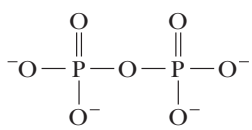
Maleic anhydride is used in the synthesis of Spandex, a fiber common in athletic wear.

Phosphoric Anhydrides

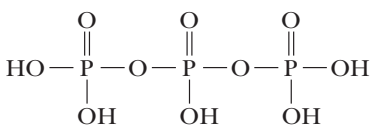
Because of the special importance of anhydrides of phosphoric acid in biochemical systems (Chapter 21), we include them here to show the similarity between them and the anhydrides of carboxylic acids. The functional group of a **phosphoric anhydride** is two phosphoryl groups bonded to an oxygen atom. Shown here are structural formulas for two anhydrides of phosphoric acid, H_3PO_4, and the ions derived by ionization of the acidic hydrogens of each:



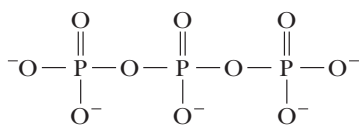
Diphosphoric acid (Pyrophosphoric acid)



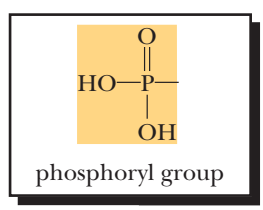
Diphosphate ion (Pyrophosphate ion)



Triphosphoric acid



Triphosphate ion



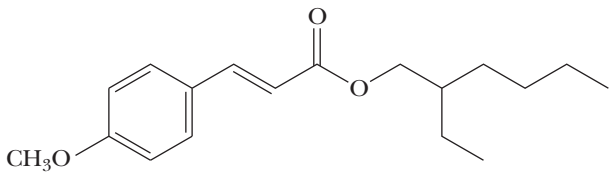
phosphoryl group

Chemical Connections 14A

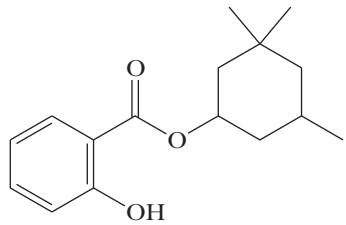
ULTRAVIOLET SUNSCREENS AND SUNBLOCKS

Ultraviolet (UV) radiation (Section 11.1, Table 11.1) penetrating the earth's ozone layer is arbitrarily divided into two regions: UVB (290–320 nm) and UVA (320–400 nm). UVB, a more energetic form of radiation than UVA, interacts directly with molecules of the skin and eyes, causing skin cancer, aging of the skin, eye damage leading to cataracts, and delayed sunburn that appears 12 to 24 hours after exposure. UVA radiation, by contrast, causes tanning. It also damages skin, albeit much less efficiently than UVB. The role of UVA in promoting skin cancer is less well understood.

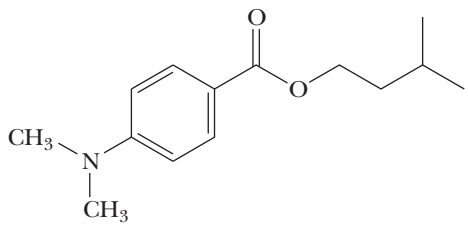
Commercial sunscreen products are rated according to their sun protection factor (SPF), which is defined as the minimum effective dose of UV radiation that produces a delayed sunburn on protected skin compared with unprotected skin. Two types of active ingredients are found in commercial sunblocks and sunscreens. The most common sunblock agent is zinc oxide, ZnO, a white crystalline substance that reflects and scatters UV radiation. Sunscreens, the second type of active ingredient, absorb UV radiation and then reradiate it as heat. Sunscreens are most effective in screening out UVB radiation, but they do not screen out UVA radiation. Thus, they allow tanning, but prevent the UVB-associated damage. Given here are structural formulas for three common esters used as UVB-screening agents, along with the name by which each is most commonly listed in the "Active Ingredients" label on commercial products:



Octyl *p*-methoxycinnamate



Homosalate



Padimate A

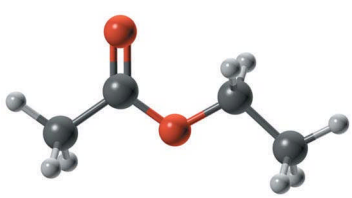
Question

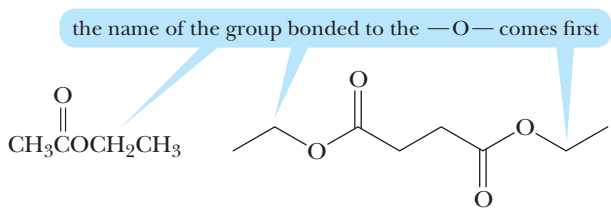
Show how each sunscreen can be synthesized from a carboxylic acid and alcohol using the Fischer esterification reaction (Section 13.6).

C. Esters and Lactones

Esters of Carboxylic Acids

The functional group of a **carboxylic ester** (commonly referred to simply as an ester) is an acyl group bonded to —OR or —OAr. Both IUPAC and common names of esters are derived from the names of the parent carboxylic acids. The alkyl or aryl group bonded to oxygen is named first, followed by the name of the acid, in which the suffix *-ic acid* is replaced by the suffix *-ate*.





Ethyl ethanoate (Ethyl acetate)

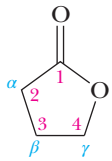
Diethyl butanedioate (Diethyl succinate)

Lactone A cyclic ester.

A cyclic ester is called a **lactone**. The IUPAC name of a lactone is formed by dropping the suffix *-oic acid* from the name of the parent carboxylic acid and adding the suffix *-olactone*. The common name is similarly derived. The location of the oxygen atom in the

ring is indicated by a number if the IUPAC name of the acid is used and by a Greek letter α, β, γ, δ, ϵ, and so forth if the common name of the acid is used.

4-Butanolactone
(A γ-lactone)

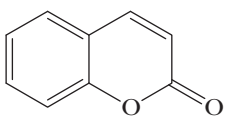


Chemical Connections 14B

FROM MOLDY CLOVER TO A BLOOD THINNER

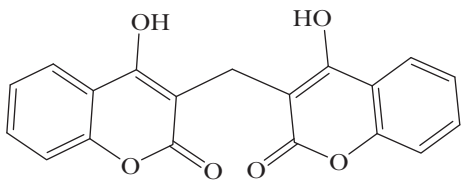
In 1933, a disgruntled farmer delivered a pail of unclotted blood to the laboratory of Dr. Karl Link at the University of Wisconsin and told tales of cows bleeding to death from minor cuts. Over the next couple of years, Link and his collaborators discovered that when cows are fed moldy clover, their blood clotting is inhibited, and they bleed to death from minor cuts and scratches. From the moldy clover, Link isolated the anticoagulant dicoumarol, a substance that delays or prevents blood from clotting. Dicoumarol exerts its anticoagulation effect by interfering with vitamin K activity (Section 20.6D). Within a few years after its discovery, dicoumarol became widely used to treat victims of heart attack and others at risk for developing blood clots.

Dicoumarol is a derivative of coumarin, a cyclic ester that gives sweet clover its pleasant smell. Coumarin, which does not interfere with blood clotting and has been used as a flavoring agent, is converted to dicoumarol as sweet clover becomes moldy. Notice that coumarin is a lactone (cyclic ester), whereas dicoumarol is a dilactone:



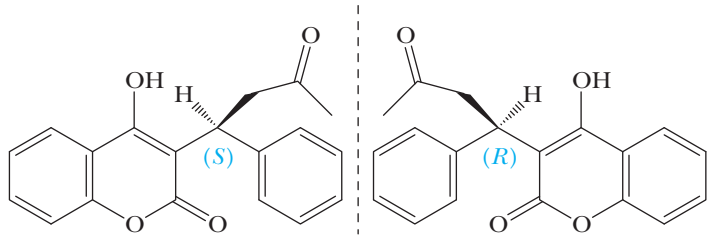
Coumarin
(from sweet clover)

as sweet clover becomes moldy →

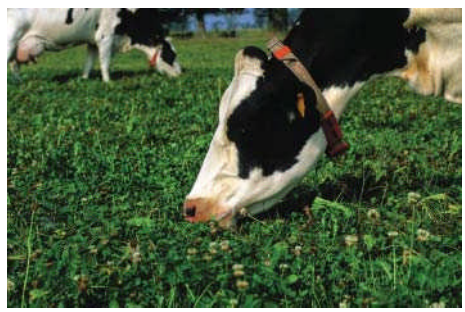


Dicoumarol
(an anticoagulant)

In a search for even more potent anticoagulants, Link developed warfarin (named after the Wisconsin Alumni Research Foundation), now used primarily as a rat poison: When rats consume warfarin, their blood fails to clot, and they bleed to death. Sold under the brand name Coumadin®, warfarin is also used as a blood thinner in humans. The *S* enantiomer is more active than the *R* enantiomer. The commercial product is a racemic mixture.



Warfarin
(a synthetic anticoagulant)



© Daniel MAR/iStockphoto

The powerful anticoagulant dicoumarol was first isolated from moldy clover.

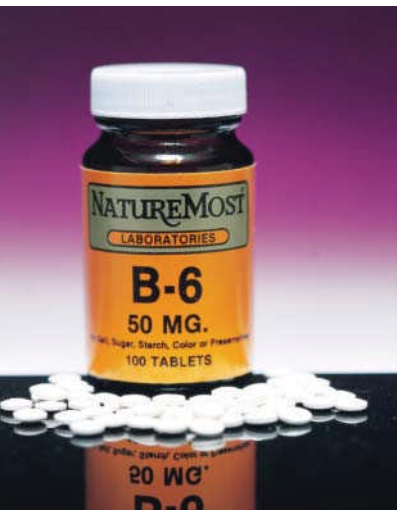
Question

Identify warfarin as an α, β, γ, etc., lactone. Identify each part of warfarin that can undergo keto–enol tautomerization and show the tautomer at that position.

Esters of Phosphoric Acid

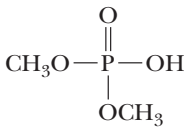
Phosphoric acid has three —OH groups and forms mono-, di-, and triphosphate esters, which are named by giving the name(s) of the alkyl or aryl group(s) bonded to oxygen, followed by the word *phosphate*—for example, dimethyl phosphate. In more complex phosphoric esters, it is common to name the organic molecule and then show the presence of the phosphoric ester by using either the word *phosphate* or the prefix *phospho-*. Following are two phosphoric esters, each of special importance in the biological world. The first reaction

Charles D. Winters

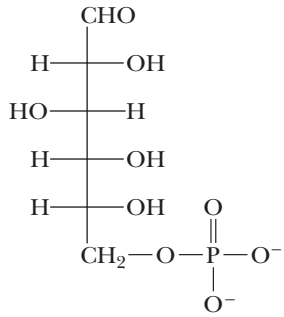


Vitamin B_6, pyridoxal.

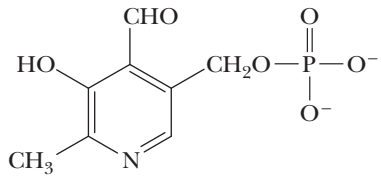
in the metabolism of glucose is the formation of a phosphoric ester of D-glucose (Section 21.3), to give D-glucose 6-phosphate. Pyridoxal phosphate is one of the metabolically active forms of vitamin B_6. Each of these esters is shown as it is ionized at pH 7.4, the pH of blood plasma; the two hydrogens of each phosphate group are ionized, giving the phosphate group a charge of –2:



Dimethyl phosphate



D-Glucose 6-phosphate



Pyridoxal phosphate

Chemical Connections 14C

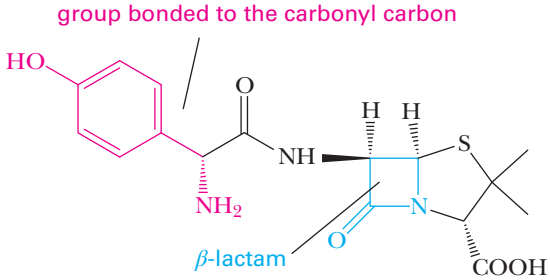
THE PENICILLINS AND CEPHALOSPORINS: β-LACTAM ANTIBIOTICS

The **penicillins** were discovered in 1928 by the Scottish bacteriologist Sir Alexander Fleming. As a result of the brilliant experimental work of Sir Howard Florey, an Australian pathologist, and Ernst Chain, a German chemist who fled Nazi Germany, penicillin G was introduced into the practice of medicine in 1943. For their pioneering work in developing one of the most effective antibiotics of all time, Fleming, Florey, and Chain were awarded the Nobel Prize in Medicine or Physiology in 1945.

The mold from which Fleming discovered penicillin was *Penicillium notatum*, a strain that gives a relatively low yield of penicillin. Commercial production of the antibiotic uses *P. chrysogenum*, a strain cultured from a mold found growing on a grapefruit in a market in Peoria, Illinois. The penicillins owe their antibacterial activity to a common mechanism that inhibits the biosynthesis of a vital part of bacterial cell walls.

The structural feature common to all penicillins is a **β-lactam** ring fused to a five-membered ring containing one S atom and one N atom (as we will see in the next section, a lactam is a cyclic amide):

The penicillins differ in the acyl group bonded to the carbonyl carbon

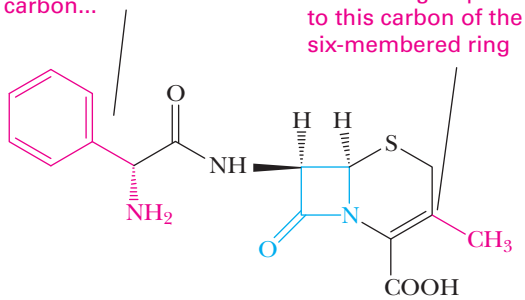


Amoxicillin
(a β-lactam antibiotic)

Soon after the penicillins were introduced into medical practice, penicillin-resistant strains of bacteria began to appear and have since proliferated. One approach to combating resistant strains is to synthesize newer, more effective penicillins. Among those that have been developed are ampicillin, methicillin, and amoxicillin. Another approach is to search for newer, more effective β-lactam antibiotics. The most effective of these discovered so far are the **cephalosporins**, the first of which was isolated from the fungus *Cephalosporium acremonium*. This class of β-lactam antibiotics has an even broader spectrum of antibacterial activity than the penicillins and is effective against many penicillin-resistant bacterial strains.

The cephalosporins differ in the acyl group bonded to the carbonyl carbon...

...and the group bonded to this carbon of the six-membered ring



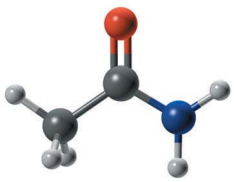
Keflex
(a β-lactam antibiotic)

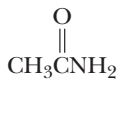
Question

What would you except to be the major form of amoxicillin present in aqueous solution at (a) pH 2.0, (b) at pH 5–6, and (c) at pH 11.0? Explain.

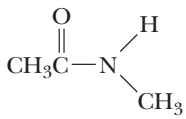
D. Amides and Lactams

The functional group of an **amide** is an acyl group bonded to a trivalent nitrogen atom. Amides are named by dropping the suffix *-oic acid* from the IUPAC name of the parent acid, or *-ic acid* from its common name, and adding *-amide*. If the nitrogen atom of an amide is bonded to an alkyl or aryl group, the group is named and its location on nitrogen is indicated by *N-*. Two alkyl or aryl groups on nitrogen are indicated by *N,N*-di- if the groups are identical or by *N*-alkyl-*N*-alkyl if they are different:

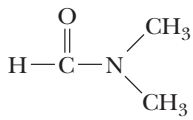




Acetamide
(a 1° amide)



N-Methylacetamide
(a 2° amide)

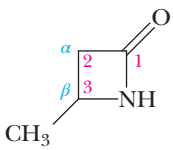


N,N-Dimethylformamide (DMF)
(a 3° amide)

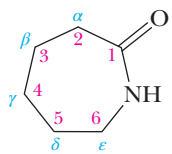
Amide bonds are the key structural feature that joins amino acids together to form polypeptides and proteins (Chapter 18).

Cyclic amides are given the special name **lactam**. Their common names are derived in a manner similar to those of lactones, with the difference that the suffix *-olactone* is replaced by *-olactam*:

Lactam A cyclic amide.



3-Butanolactam
(A β-lactam)

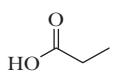
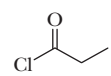
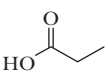
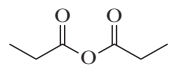
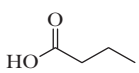
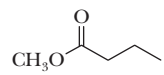
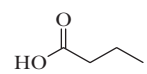
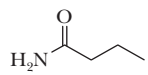


6-Hexanolactam
(An ε-lactam)

6-Hexanolactam is a key intermediate in the synthesis of nylon-6 (Section 16.4A).

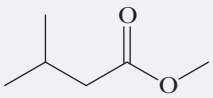
HOW TO 14.1 Name Functional Derivatives of Carboxylic Acids

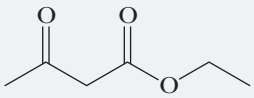
The key to naming one of the four main functional derivatives of carboxylic acids is to realize how its name differs from that of the corresponding carboxylic acid. The following table highlights the difference for each derivative in italics.

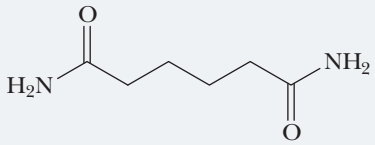
Functional Derivative	Carboxylic Acid Name	Derivative Name	Example
acid halide	alkanoic *acid*	alkanoyl *halide*	 propanoic acid  propanoyl chloride
acid anhydride	alkanoic *acid*	alkanoic *anhydride*	 propanoic acid  propanoic anhydride
ester	alkanoic *acid*	*alkyl* alkano*ate*	 butanoic acid  methyl butanoate
amide	alkanoic *acid*	alkan*amide*	 butanoic acid  butanamide

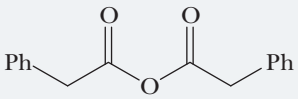
EXAMPLE 14.1

Write the IUPAC name for each compound:

(a) 

(b) 

(c) 

(d) 

STRATEGY

Identify the longest chain containing the functional derivative to establish the root name. Treat the molecule as if each functional derivative group were a carboxyl group and name it as a carboxylic acid. Then change the suffix of the name to reflect the derivative. See HowTo 14.1 for examples.

SOLUTION

Given first are IUPAC names and then, in parentheses, common names:

(a) Methyl 3-methylbutanoate (methyl isovalerate, from isovaleric acid)
(b) Ethyl 3-oxobutanoate (ethyl β-ketobutyrate, from β-ketobutyric acid)
(c) Hexanediamide (adipamide, from adipic acid)
(d) Phenylethanoic anhydride (phenylacetic anhydride, from phenylacetic acid)

See problems 14.9–14.11

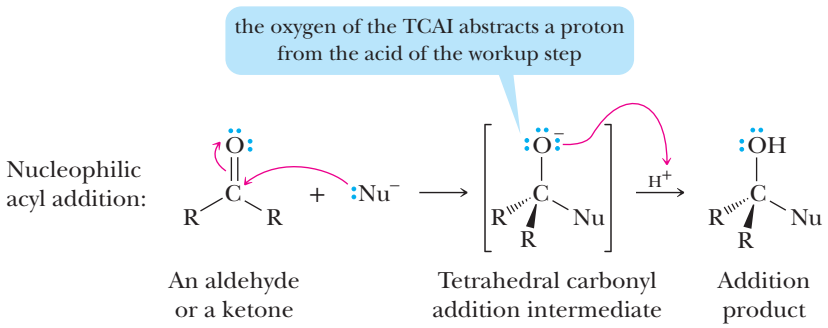
PROBLEM 14.1

Draw a structural formula for each compound:

(a) *N*-Cyclohexylacetamide
(b) *sec*-Butyl acetate
(c) Cyclobutyl butanoate
(d) *N*-(2-Octyl)benzamide
(e) Diethyl adipate
(f) Propanoic anhydride

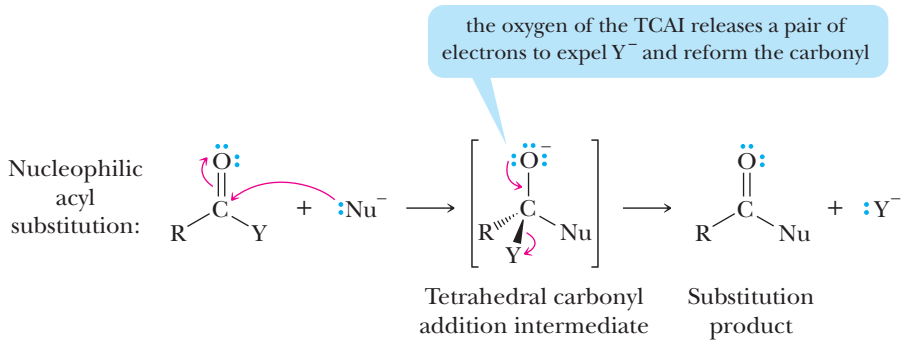
14.2 What Are the Characteristic Reactions of Carboxylic Acid Derivatives?

The most common reaction theme of acid halides, anhydrides, esters, and amides is the addition of a nucleophile to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate. To this extent, the reactions of these functional groups are similar to nucleophilic addition to the carbonyl groups in aldehydes and ketones (Section 12.4). The **tetrahedral carbonyl addition intermediate** (TCAI) formed from an aldehyde or a ketone then adds H^+. The result of this reaction is nucleophilic addition to a carbonyl group of an aldehyde or a ketone:



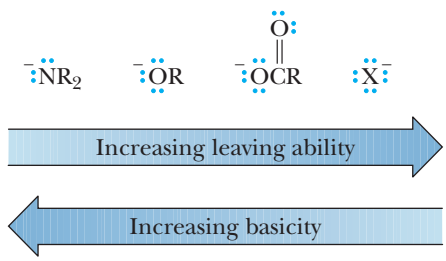
For functional derivatives of carboxylic acids, the fate of the tetrahedral carbonyl addition intermediate is quite different from that of aldehydes and ketones. This intermediate collapses to expel the leaving group and regenerate the carbonyl group. The result of this addition–elimination sequence is **nucleophilic acyl substitution**:

Nucleophilic acyl substitution A reaction in which a nucleophile bonded to a carbonyl carbon is replaced by another nucleophile.

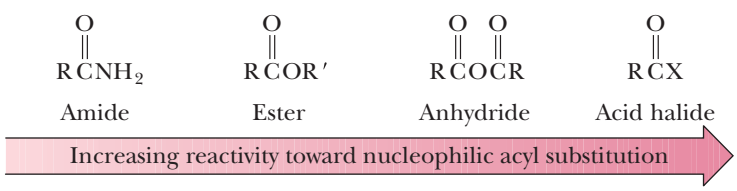


The major difference between these two types of carbonyl addition reactions is that aldehydes and ketones do not have a group, Y, that can leave as a stable anion. They undergo only nucleophilic acyl addition. The four carboxylic acid derivatives we study in this chapter do have a group, Y, that can leave as a stable anion; accordingly, they undergo nucleophilic acyl substitution.

In this general reaction, we show the nucleophile and the leaving group as anions. That need not be the case, however. Neutral molecules, such as water, alcohols, ammonia, and amines, may also serve as nucleophiles in the acid-catalyzed version of the reaction. We show the leaving groups here as anions to illustrate an important point about leaving groups, namely, that the weaker the base, the better is the leaving group (Section 7.5C):



The weakest base in this series, and thus the best leaving group, is halide ion; acid halides are the most reactive toward nucleophilic acyl substitution. The strongest base, and hence the poorest leaving group, is amide ion; amides are the least reactive toward nucleophilic acyl substitution. Acid halides and acid anhydrides are so reactive that they are not found in nature. Esters and amides, however, are universally present.

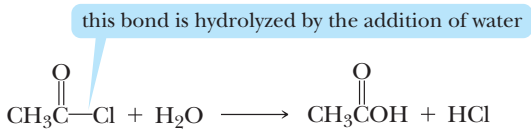


14.3 What Is Hydrolysis?

Hydrolysis (Greek: *hydor*, water; *lyein*, separate) is a chemical process whereby a bond (or bonds) in a molecule is broken by its reaction with water. In hydrolysis, the water molecule is also typically split into H^+ and OH^-.

A. Acid Chlorides

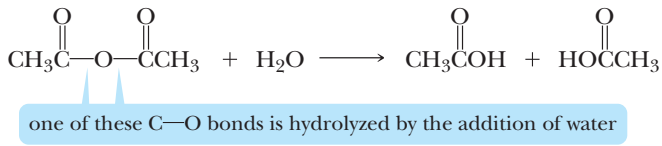
Low-molecular-weight acid chlorides react very rapidly with water to form carboxylic acids and HCl:



Higher-molecular-weight acid chlorides are less soluble and consequently react less rapidly with water.

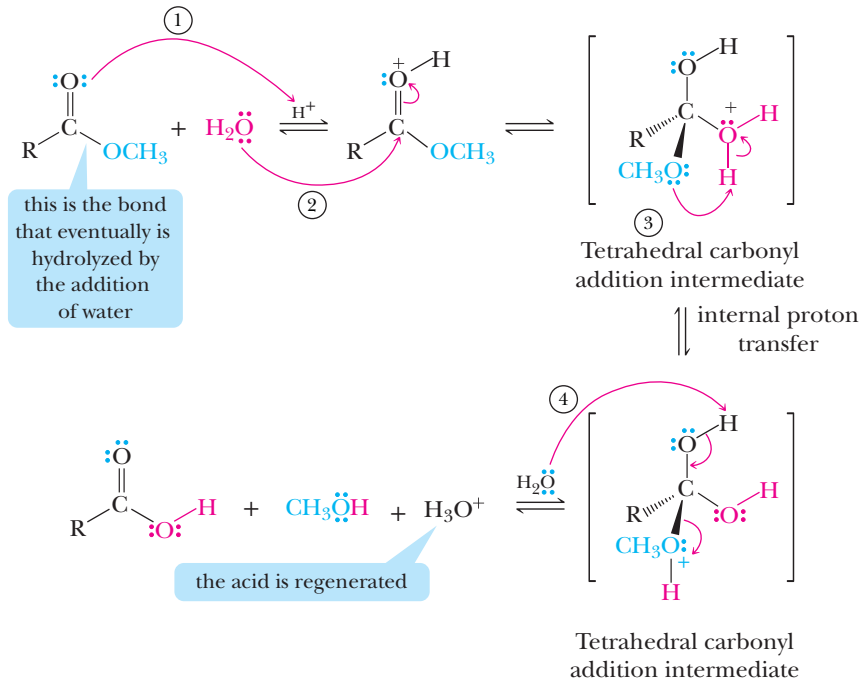
B. Acid Anhydrides

Acid anhydrides are generally less reactive than acid chlorides. The lower-molecular-weight anhydrides, however, react readily with water to form two carboxylic acids:



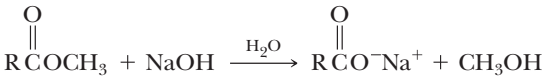
C. Esters

Esters are hydrolyzed only very slowly, even in boiling water. Hydrolysis becomes considerably more rapid, however, when esters are refluxed in aqueous acid or base. When we discussed acid-catalyzed (Fischer) esterification in Section 13.6, we pointed out that esterification is an equilibrium reaction. Hydrolysis of esters in aqueous acid is also an equilibrium reaction and proceeds by the same mechanism as esterification, except in reverse. The role of the acid catalyst is to protonate the carbonyl oxygen **(Step 1: Add a proton)**, thereby increasing the electrophilic character of the carbonyl carbon toward attack by water **(Step 2: Reaction of a nucleophile and an electrophile to form a new covalent bond)** to form a tetrahedral carbonyl addition intermediate. An internal proton transfer to the alkoxy group **(Step 3: Internal proton transfer)** makes that group a good leaving group and allows the collapse of this intermediate **(Step 4: Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group)** to give a carboxylic acid and an alcohol. In this reaction, acid is a catalyst; it is consumed in the first step, but another is generated at the end of the reaction:



Hydrolysis of esters may also be carried out with hot aqueous base, such as aqueous NaOH. Hydrolysis of esters in aqueous base is often called **saponification**, a reference to the use of this reaction in the manufacture of soaps (Section 19.2A). Each mole of ester hydrolyzed requires one mole of base, as shown in the following balanced equation:

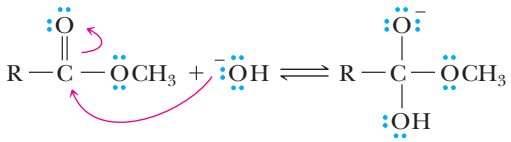
Saponification Hydrolysis of an ester in aqueous NaOH or KOH to an alcohol and the sodium or potassium salt of a carboxylic acid.



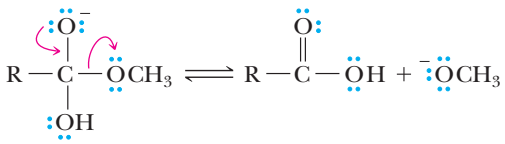
Mechanism

Hydrolysis of an Ester in Aqueous Base

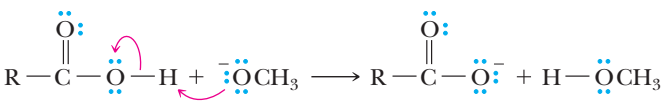
STEP 1: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Addition of hydroxide ion to the carbonyl carbon of the ester gives a tetrahedral carbonyl addition intermediate:



STEP 2: *Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group.*
Collapse of this intermediate gives a carboxylic acid and an alkoxide ion:



STEP 3: *Take a proton away.*
Proton transfer from the carboxyl group (an acid) to the alkoxide ion (a base) gives the carboxylate anion. This step is irreversible because the alcohol is not a strong enough nucleophile to attack a carboxylate anion:

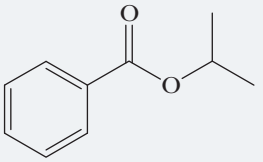
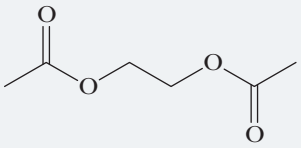


There are two major differences between the hydrolysis of esters in aqueous acid and that in aqueous base:

1. For hydrolysis in aqueous acid, acid is required in only catalytic amounts. For hydrolysis in aqueous base, base is required in equimolar amounts, because it is a reactant, not just a catalyst.
2. Hydrolysis of an ester in aqueous acid is reversible. Hydrolysis in aqueous base is irreversible because a carboxylic acid anion is not attacked by ROH.

EXAMPLE 14.2

Complete and balance equations for the hydrolysis of each ester in aqueous sodium hydroxide, showing all products as they are ionized in aqueous NaOH:

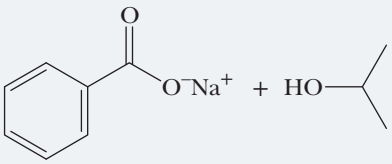
(a)  + NaOH $\xrightarrow{H_2O}$ **(b)**  + 2 NaOH $\xrightarrow{H_2O}$

STRATEGY

The hydrolysis of an ester results in a carboxyl group and an alcohol for every ester group in the molecule. In aqueous base, one mole of NaOH is consumed for every ester group in the molecule.

SOLUTION

The products of hydrolysis of (a) are benzoic acid and 2-propanol. In aqueous NaOH, benzoic acid is converted to its sodium salt. Therefore, one mole of NaOH is required for the hydrolysis of one mole of this ester. Compound (b) is a diester of ethylene glycol. Two moles of NaOH are required for its hydrolysis:

(a) 

Sodium benzoate — 2-Propanol (Isopropyl alcohol)

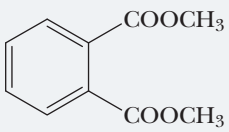
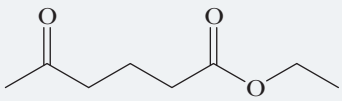
(b) $2\ CH_3CO^-Na^+$ + $HOCH_2CH_2OH$

Sodium acetate — 1,2-Ethanediol (Ethylene glycol)

See problems 14.19, 14.20, 14.31

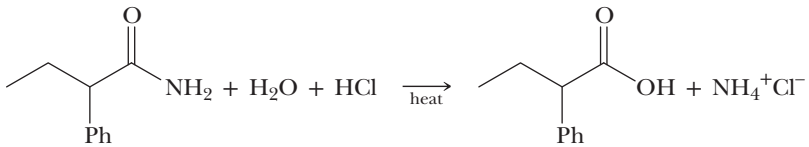
PROBLEM 14.2

Complete and balance equations for the hydrolysis of each ester in aqueous solution, showing each product as it is ionized under the given experimental conditions:

(a)  + NaOH (excess) $\xrightarrow{H_2O}$ **(b)**  + H_2O $\xrightarrow{HCl}$

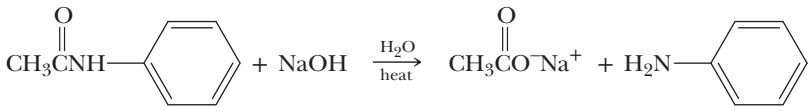
D. Amides

Amides require considerably more vigorous conditions for hydrolysis in both acid and base than do esters. Amides undergo hydrolysis in hot aqueous acid to give a carboxylic acid and ammonia. Hydrolysis is driven to completion by the acid–base reaction between ammonia or the amine and acid to form an ammonium salt. One mole of acid is required per mole of amide:



2-Phenylbutanamide — 2-Phenylbutanoic acid

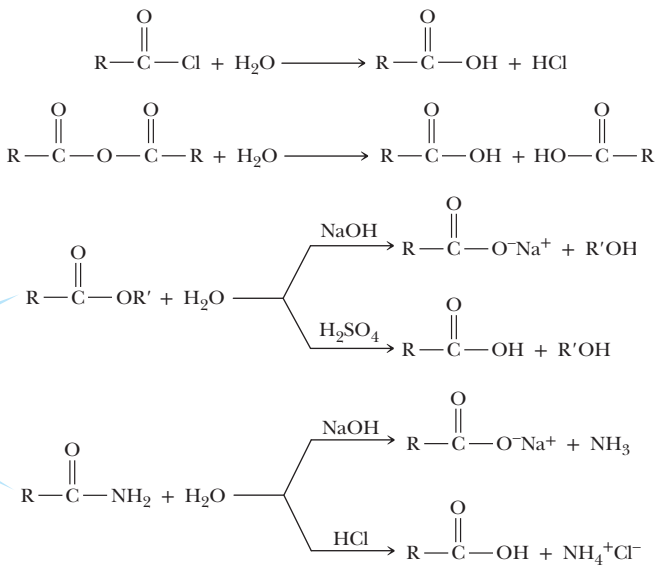
In aqueous base, the products of amide hydrolysis are a carboxylate ion and ammonia or an amine. Base-catalyzed hydrolysis is driven to completion by the acid–base reaction between the carboxylic acid and base to form a salt. One mole of base is required per mole of amide:



N-Phenylethanamide (*N*-Phenylacetamide, Acetanilide) | Sodium acetate | Aniline

The reactions of these functional groups with water are summarized in Table 14.1. Remember that, although all four functional groups react with water, there are large differences in the rates and experimental conditions under which they undergo hydrolysis.

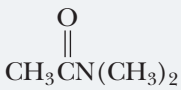
TABLE 14.1 Summary of Reaction of Acid Chlorides, Anhydrides, Esters, and Amides with Water

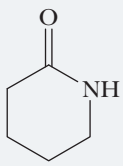


esters and amides require acidic or basic conditions to be hydrolyzed

EXAMPLE 14.3

Write equations for the hydrolysis of these amides in concentrated aqueous HCl, showing all products as they exist in aqueous HCl and showing the number of moles of HCl required for the hydrolysis of each amide:

(a) 

(b) 

STRATEGY

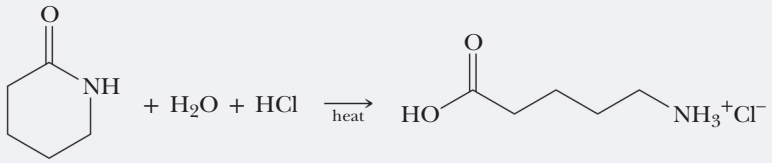
The hydrolysis of an amide results in a carboxyl group and an ammonium chloride salt for every amide group in the molecule. Either one mole of NaOH (basic conditions) or one mole of HCl (acidic conditions) is consumed for every amide group in the molecule.

SOLUTION

(a) Hydrolysis of *N,N*-dimethylacetamide gives acetic acid and dimethylamine. Dimethylamine, a base, is protonated by HCl to form dimethylammonium ion and is shown in the balanced equation as dimethylammonium chloride. Complete hydrolysis of this amide requires one mole of HCl for each mole of the amide:

$$CH_3CN(CH_3)_2 + H_2O + HCl \xrightarrow{\text{heat}} CH_3COH + (CH_3)_2NH_2^+Cl^-$$

(b) Hydrolysis of this δ-lactam gives the protonated form of 5-aminopentanoic acid. One mole of acid is required per mole of lactam:

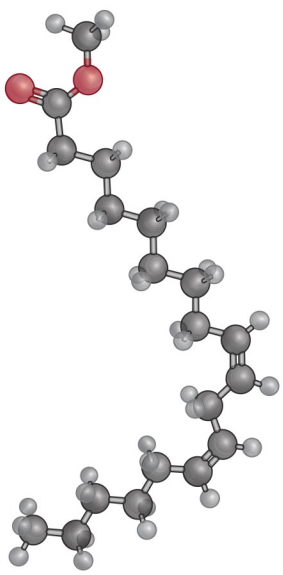


See problems 14.29, 14.32

PROBLEM 14.3

Complete equations for the hydrolysis of the amides in Example 14.3 in concentrated aqueous NaOH. Show all products as they exist in aqueous NaOH, and show the number of moles of NaOH required for the hydrolysis of each amide.

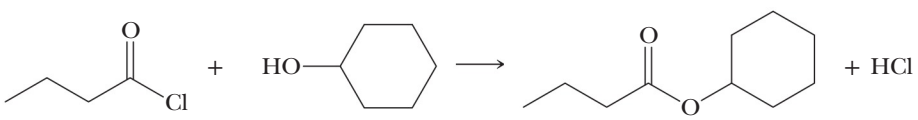
14.4 How Do Carboxylic Acid Derivatives React with Alcohols?



Methyl linoleate is used as a biodiesel fuel and is synthesized using transesterification reactions (Problem 14.54).

A. Acid Chlorides

Acid chlorides react with alcohols to give an ester and HCl:



Butanoyl chloride Cyclohexanol Cyclohexyl butanoate

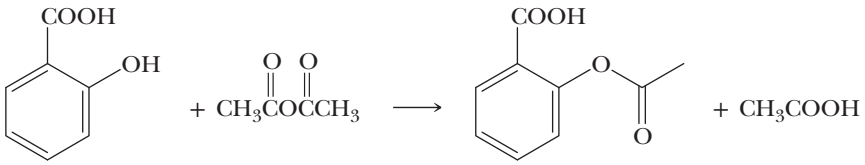
Because acid chlorides are so reactive toward even weak nucleophiles such as alcohols, no catalyst is necessary for these reactions. Phenol and substituted phenols also react with acid chlorides to give esters.

B. Acid Anhydrides

Acid anhydrides react with alcohols to give one mole of ester and one mole of a carboxylic acid.

$$\underset{\text{Acetic anhydride}}{CH_3COCCH_3} + \underset{\text{Ethanol}}{HOCH_2CH_3} \longrightarrow \underset{\text{Ethyl acetate}}{CH_3COCH_2CH_3} + \underset{\text{Acetic acid}}{CH_3COH}$$

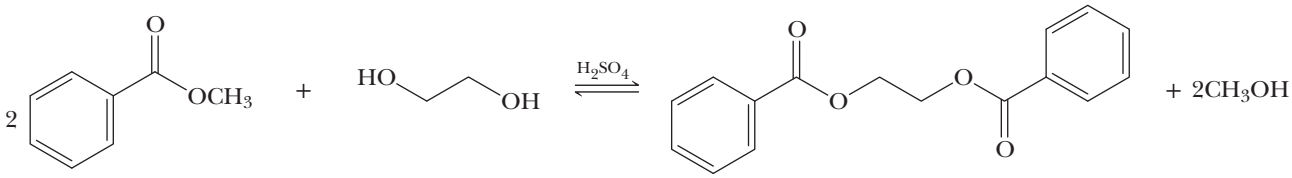
Thus, the reaction of an alcohol with an anhydride is a useful method for synthesizing esters. Aspirin is synthesized on an industrial scale by reacting acetic anhydride with salicylic acid:



2-Hydroxybenzoic acid (Salicylic acid) | Acetic anhydride | Acetylsalicylic acid (Aspirin) | Acetic acid

C. Esters

When treated with an alcohol in the presence of an acid catalyst, esters undergo an exchange reaction called **transesterification**. In this reaction, the original —OR group of the ester is exchanged for a new —OR group. In the following example, the transesterification can be driven to completion by heating the reaction at a temperature above the boiling point of methanol (65 °C) so that methanol distills from the reaction mixture:



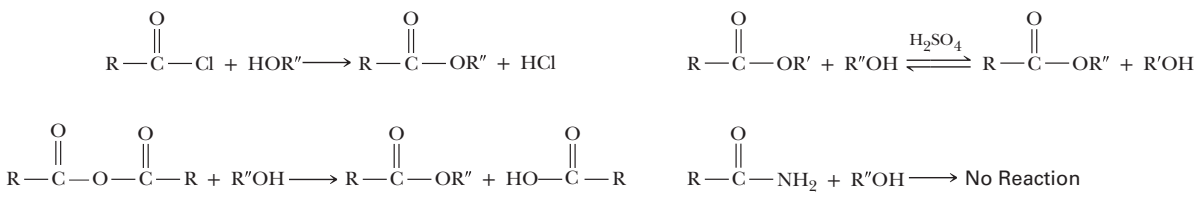
Methyl benzoate | 1,2-Ethanediol (Ethylene glycol) | (A diester of ethylene glycol)

D. Amides

Amides do not react with alcohols under any experimental conditions. Alcohols are not strong enough nucleophiles to attack the carbonyl group of an amide.

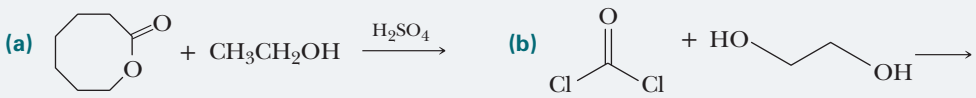
The reactions of the foregoing functional groups with alcohols are summarized in Table 14.2. As with reactions of these same functional groups with water (Section 14.3), there are large differences in the rates and experimental conditions under which they undergo reactions with alcohols. At one extreme are acid chlorides and anhydrides, which react rapidly; at the other extreme are amides, which do not react at all.

TABLE 14.2 Summary of Reaction of Acid Chlorides, Anhydrides, Esters, and Amides with Alcohols



EXAMPLE 14.4

Complete these equations:

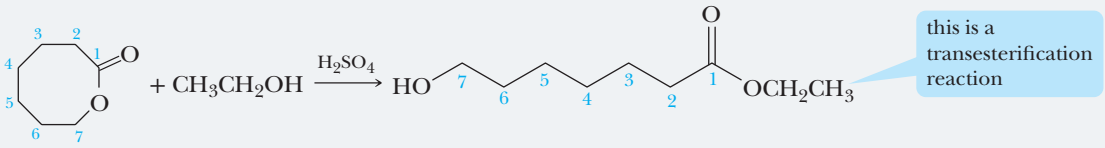


STRATEGY

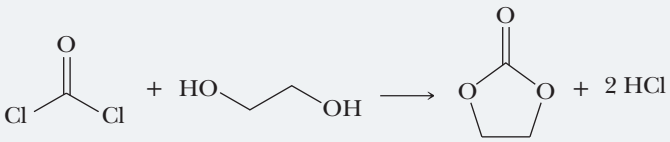
Acid halides, anhydrides, and esters undergo nucleophilic acyl substitution with alcohols (HOR′), the net result being the replacement of each —X, —OC(O)R, or —OR group with the —OR′ group of the alcohol.

SOLUTION

(a)



(b)

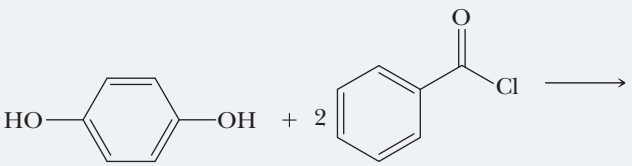


See problems 14.16, 14.17, 14.19–14.22, 14.28

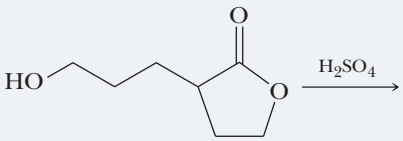
PROBLEM 14.4

Complete these equations (the stoichiometry of each is given in the equation):

(a)



(b)

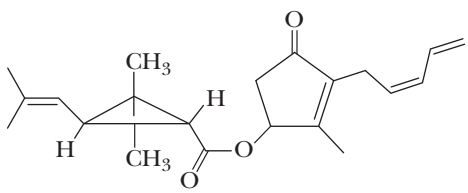


Chemical Connections 14D

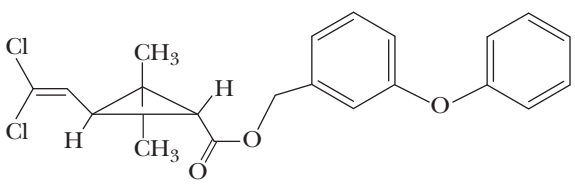
THE PYRETHRINS: NATURAL INSECTICIDES OF PLANT ORIGIN

Pyrethrum is a natural insecticide obtained from the powdered flower heads of several species of *Chrysanthemum*, particularly *C. cinerariaefolium*. The active substances in pyrethrum, principally pyrethrins I and II, are contact poisons for insects and cold-blooded vertebrates. Because their concentrations in the pyrethrum powder used in chrysanthemum-based insecticides are nontoxic to plants and higher animals, pyrethrum powder is used in household and livestock sprays, as well as in dusts for edible plants. Natural pyrethrins are esters of chrysanthemic acid.

While pyrethrum powders are effective insecticides, the active substances in them are destroyed rapidly in the environment. In an effort to develop synthetic compounds as effective as these natural insecticides but with greater biostability, chemists have prepared a series of esters related in structure to chrysanthemic acid. Permethrin is one of the most commonly used synthetic pyrethrinlike compounds in household and agricultural products.



Pyrethrin I



Permethrin

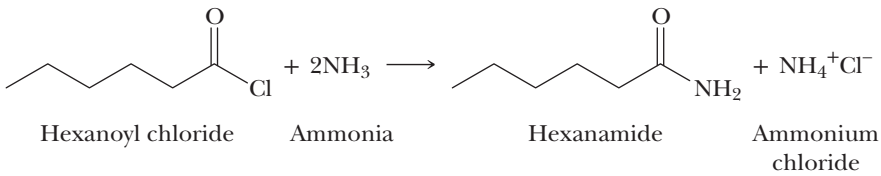
Question

Show the compounds that would result if pyrethrin I and permethrin were to undergo hydrolysis.

14.5 How Do Carboxylic Acid Derivatives React with Ammonia and Amines?

A. Acid Chlorides

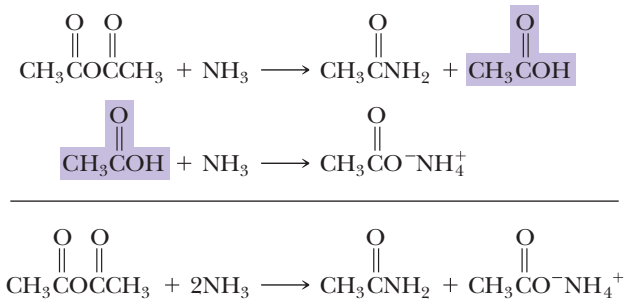
Acid chlorides react readily with ammonia and with 1° and 2° amines to form amides. Complete conversion of an acid chloride to an amide requires two moles of ammonia or amine: one to form the amide and one to neutralize the hydrogen chloride formed:



Hexanoyl chloride — Ammonia — Hexanamide — Ammonium chloride

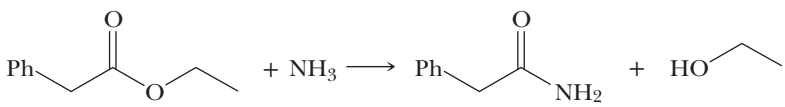
B. Acid Anhydrides

Acid anhydrides react with ammonia and with 1° and 2° amines to form amides. As with acid chlorides, two moles of ammonia or amine are required—one to form the amide and one to neutralize the carboxylic acid by-product. To help you see what happens, this reaction is broken into two steps, which, when added together, give the net reaction for the reaction of an anhydride with ammonia:



C. Esters

Esters react with ammonia and with 1° and 2° amines to form amides:



Ethyl phenylacetate — Phenylacetamide — Ethanol

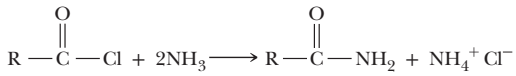
Because an alkoxide anion is a poor leaving group compared with a halide or carboxylate ion, esters are less reactive toward ammonia, 1° amines, and 2° amines than are acid chlorides or acid anhydrides.

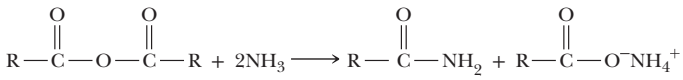
D. Amides

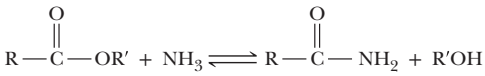
Amides do not react with ammonia or amines.

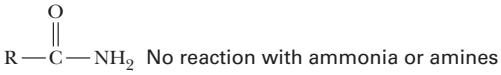
The reactions of the preceding four functional groups with ammonia and amines are summarized in Table 14.3.

TABLE 14.3 Summary of Reaction of Acid Chlorides, Anhydrides, Esters, and Amides with Ammonia and Amines





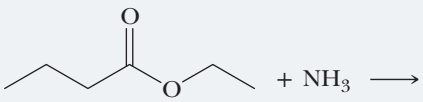




EXAMPLE 14.5

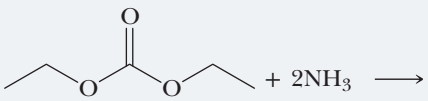
Complete these equations (the stoichiometry of each is given in the equation):

(a)



Ethyl butanoate

(b)



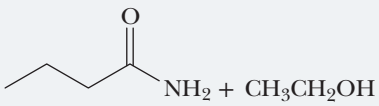
Diethyl carbonate

STRATEGY

Acid halides, anhydrides, and esters undergo nucleophilic acyl substitution with ammonia or amines, the net result being the replacement of each —X, —OC(O)R, or —OR group with the $—NH_2$ group of ammonia or the —NHR or $—NR_2$ group of the amine.

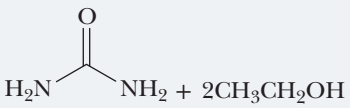
SOLUTION

(a)



Butanamide

(b)



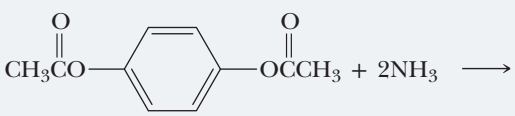
Urea

See problems 14.18–14.22, 14.24–14.26, 14.31, 14.35

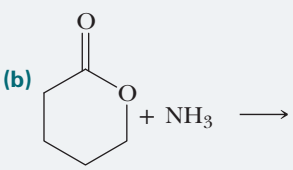
PROBLEM 14.5

Complete these equations (the stoichiometry of each is given in the equation):

(a)

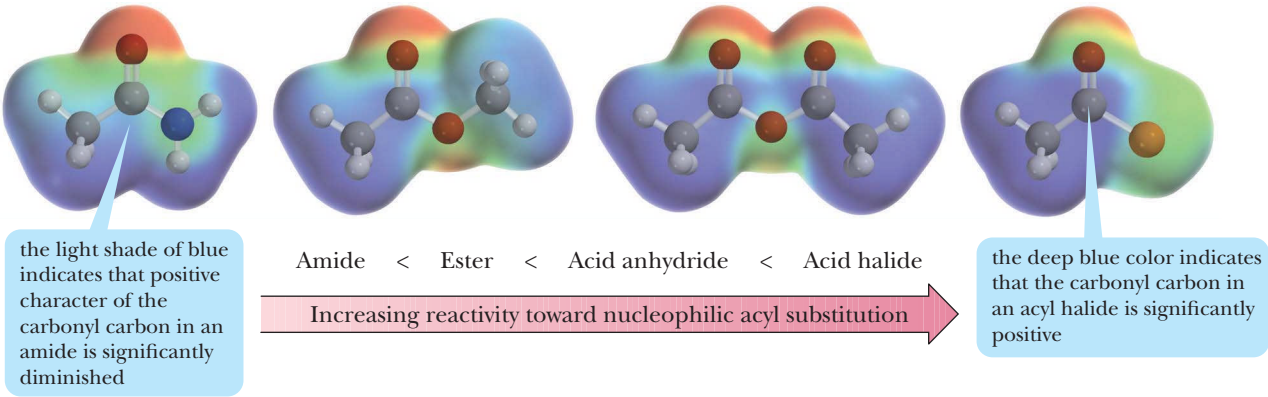


(b)



14.6 How Can Functional Derivatives of Carboxylic Acids Be Interconverted?

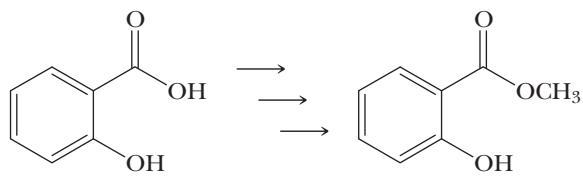
In the last few sections, we have seen that acid chlorides are the most reactive carboxyl derivatives toward nucleophilic acyl substitution and that amides are the least reactive:



Chemical Connections 14E

SYSTEMATIC ACQUIRED RESISTANCE IN PLANTS

The use of germicides to protect plants from harmful pathogens is common in farming. Recently, plant physiologists discovered that some plant species are able to generate their own defenses against pathogens. The tobacco mosaic virus (TMV), for example, is a particularly devastating pathogen for plants such as tobacco, cucumber, and tomato. Scientists have found that certain strains of these plants produce large amounts of salicylic acid upon being infected with TMV. Accompanying the infection is the appearance of lesions on the leaves of the plants, which help to contain the infection to those localized areas. Furthermore, scientists have discovered that neighboring plants tend to acquire some resistance to TMV. It appears that the infected plant somehow signals neighboring plants of the impending danger by converting salicylic acid to its ester, methyl salicylate:



Salicylic acid Methyl salicylate

With a lower boiling point and higher vapor pressure than salicylic acid has, the methyl salicylate diffuses into the air from the infected plant, and the surrounding plants use it as a signal to enhance their defenses against TMV.

The tobacco plant, *Nicotiana tobacum*.

Question

An early proposal in this research was that the tobacco plant could utilize two molecules of salicylic acid (molar mass 138.12 g/mol) in a nucleophilic acyl substitution reaction to yield a compound with a molar mass of 240.21 g/mol that would be less polar than salicylic acid. Propose a structure for this reaction product.

Another useful way to think about the relative reactivities of these four functional derivatives of carboxylic acids is summarized in Figure 14.1. Any functional group in this figure can be prepared from any functional group above it by treatment with an appropriate oxygen or nitrogen nucleophile. An acid chloride, for example, can be converted to an acid

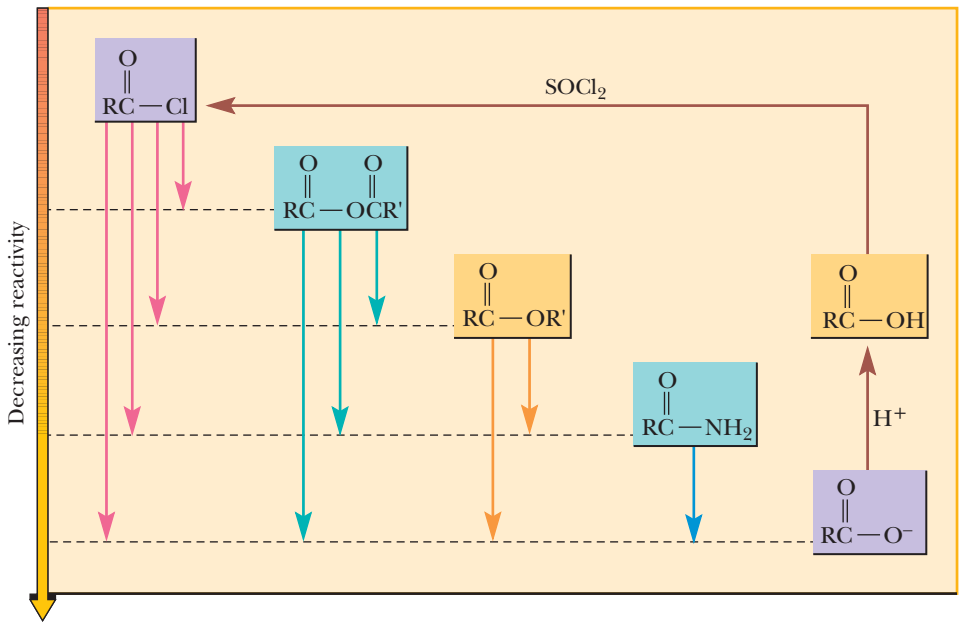


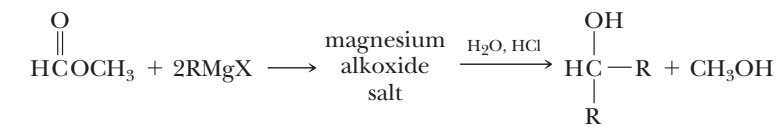
FIGURE 14.1 Relative reactivities of carboxylic acid derivatives toward nucleophilic acyl substitution. A more reactive derivative may be converted to a less reactive derivative by treatment with an appropriate reagent. Treatment of a carboxylic acid with thionyl chloride converts the carboxylic acid to the more reactive acid chloride. Carboxylic acids are about as reactive as esters under acidic conditions, but are converted to the unreactive carboxylate anions under basic conditions.

anhydride, an ester, an amide, or a carboxylic acid. An acid anhydride, ester, or amide, however, does not react with chloride ion to give an acid chloride.

Notice that all carboxylic acid derivatives can be converted to carboxylic acids, which in turn can be converted to acid chlorides. Thus, any acid derivative can be used to synthesize another, either directly or via a carboxylic acid.

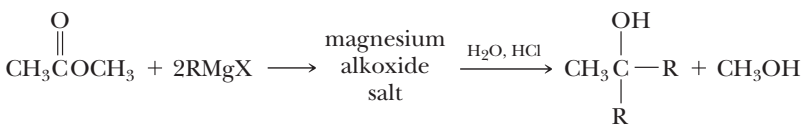
14.7 How Do Esters React with Grignard Reagents?

Treating a formic ester with two moles of a Grignard reagent, followed by hydrolysis of the magnesium alkoxide salt in aqueous acid, gives a 2° alcohol, whereas treating an ester other than a formate with a Grignard reagent gives a 3° alcohol in which two of the groups bonded to the carbon bearing the —OH group are the same:



An ester of formic acid

A 2° alcohol



An ester other than formic acid

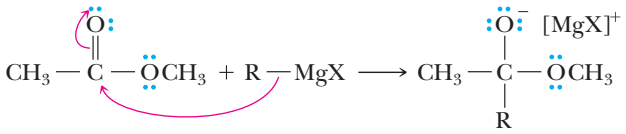
A 3° alcohol

Reaction of an ester with a Grignard reagent involves the formation of two successive tetrahedral carbonyl addition compounds. The first collapses to give a new carbonyl compound—an aldehyde from a formic ester, a ketone from all other esters. The second intermediate is stable and, when protonated, gives the final alcohol. It is important to realize that it is not possible to use RMgX and an ester to prepare an aldehyde or a ketone: The intermediate aldehyde or ketone is more reactive than the ester and reacts immediately with the Grignard reagent to give a tertiary alcohol.

Mechanism

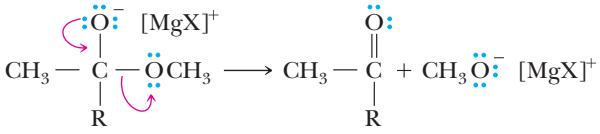
Reaction of an Ester with a Grignard Reagent

STEP 1: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
Reaction begins with the addition of 1 mole of Grignard reagent to the carbonyl carbon to form a tetrahedral carbonyl addition intermediate:



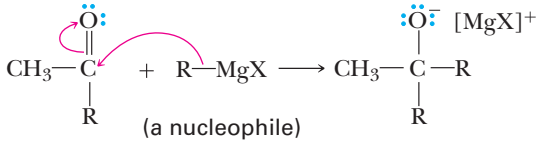
(an electrophile) (a nucleophile) A magnesium salt (a tetrahedral carbonyl addition intermediate)

STEP 2: *Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group.*
This intermediate then collapses to give a new carbonyl-containing compound and a magnesium alkoxide salt:



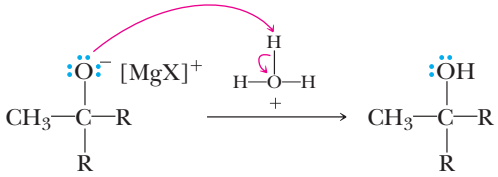
A ketone

STEP 3: *Reaction of a nucleophile and an electrophile to form a new covalent bond.*
The new carbonyl-containing compound reacts with a second mole of Grignard reagent to form a second tetrahedral carbonyl addition compound:



A ketone (an electrophile) (a nucleophile) Magnesium salt

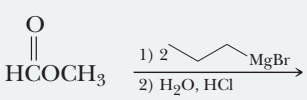
STEP 4: *Add a proton.*
Workup in aqueous acid gives a 3° alcohol (or a 2° alcohol if the starting ester was a formate):

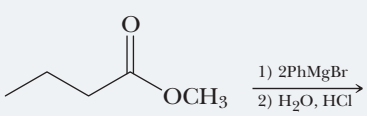


Magnesium salt A 3° alcohol

EXAMPLE 14.6

Complete each Grignard reaction:

(a) 

(b) 

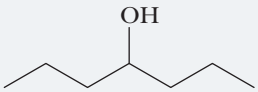
STRATEGY

Reaction of a Grignard reagent with an ester results in an alcohol containing two identical R groups (the R groups from the Grignard reagent) bonded to the former carbonyl carbon.

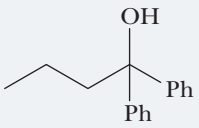
SOLUTION

Sequence (a) gives a 2° alcohol, and sequence (b) gives a 3° alcohol:

(a)



(b)

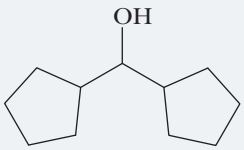


See problems 14.30, 14.33, 14.34

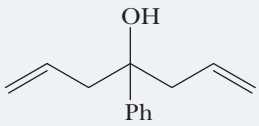
PROBLEM 14.6

Show how to prepare each alcohol by treating an ester with a Grignard reagent:

(a)



(b)

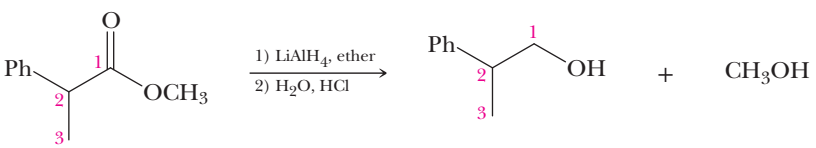


14.8 How Are Derivatives of Carboxylic Acids Reduced?

Most reductions of carbonyl compounds, including aldehydes and ketones, are now accomplished by transferring hydride ions from boron or aluminum hydrides. We have already seen the use of sodium borohydride to reduce the carbonyl groups of aldehydes and ketones to hydroxyl groups (Section 12.10B). We have also seen the use of lithium aluminum hydride to reduce not only the carbonyl groups of aldehydes and ketones, but also carboxyl groups (Section 13.5A), to hydroxyl groups.

A. Esters

An ester is reduced by lithium aluminum hydride to two alcohols. The alcohol derived from the acyl group is primary:

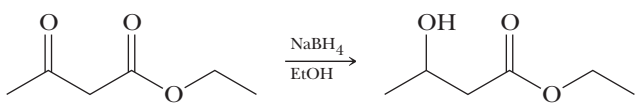


Methyl 2-phenylpropanoate

2-Phenyl-1-propanol (a 1° alcohol)

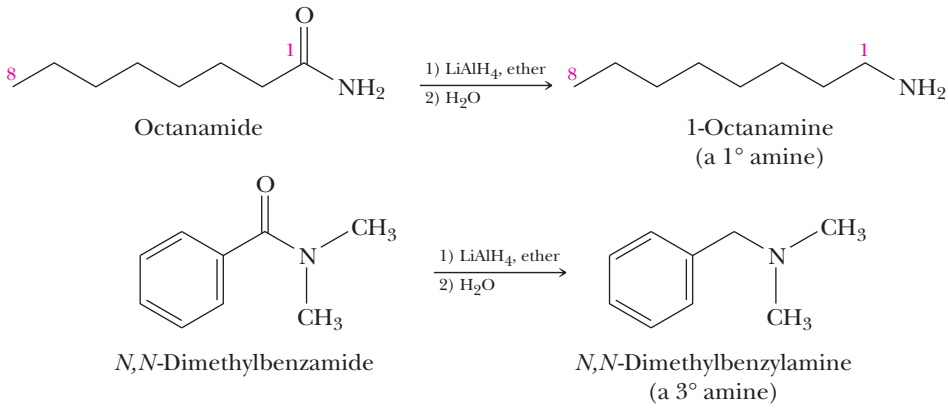
Methanol

Sodium borohydride is not normally used to reduce esters because the reaction is very slow. Because of this lower reactivity of sodium borohydride toward esters, it is possible to reduce the carbonyl group of an aldehyde or a ketone to a hydroxyl group with this reagent without reducing an ester or a carboxyl group in the same molecule:



B. Amides

Reduction of amides by lithium aluminum hydride can be used to prepare 1°, 2°, or 3° amines, depending on the degree of substitution of the amide:



Octanamide

1-Octanamine
(a 1° amine)

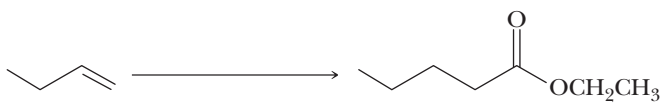
N,N-Dimethylbenzamide

N,N-Dimethylbenzylamine
(a 3° amine)

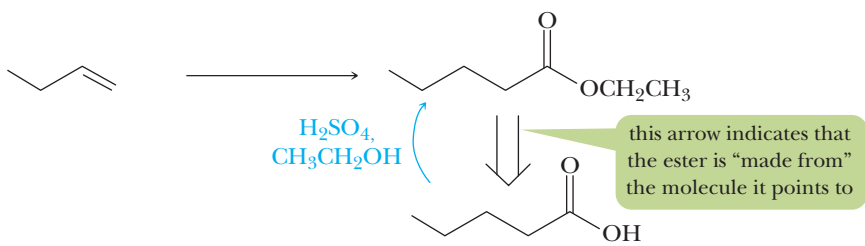
Approach Multistep Synthesis Problems

HOW TO 14.2

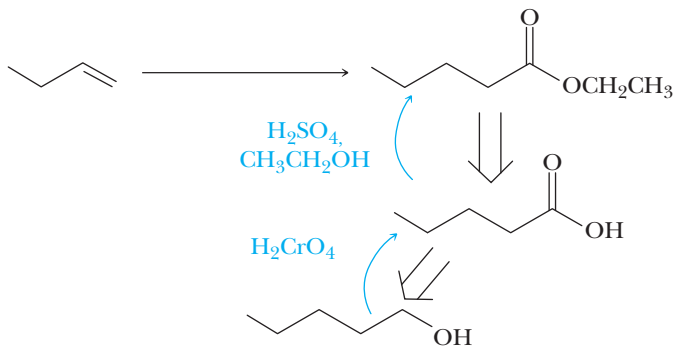
(a) When a given chemical transformation cannot be achieved with a known chemical reaction, it is necessary to use multiple steps to complete the synthesis. One of the most effective ways to accomplish this is through retrosynthetic analysis. The technique, formalized by Harvard Professor and Nobel Laureate E. J. Corey, involves working backwards from a target molecule until the synthesis is achieved. The technique is illustrated using the following transformation:



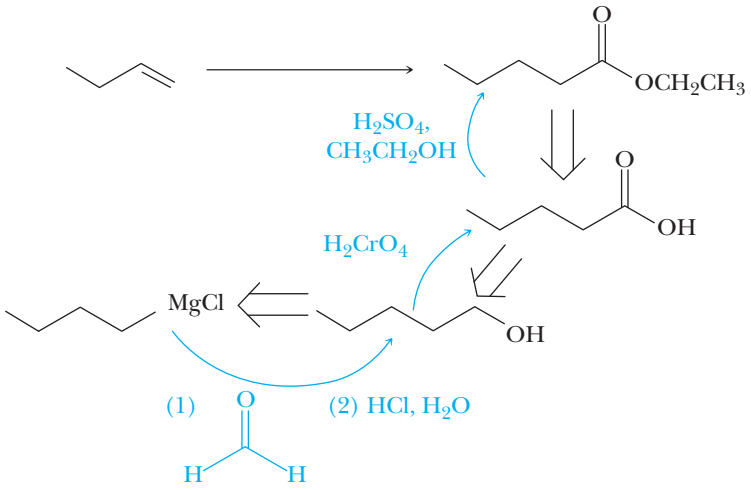
(b) Because there is no reaction that converts an alkene into an ester while also forming a new C—C bond, we work backwards from the ester. The goal is to identify a reaction (or reactions) that can synthesize esters. One such reaction is the Fischer esterification:



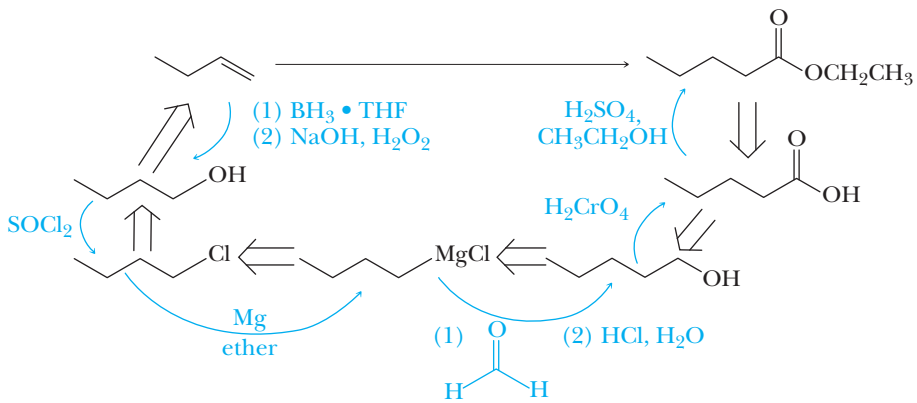
(c) Now that we've proposed that the ester can be made from pentanoic acid via Fischer esterification, the next step is to identify a reaction that can produce pentanoic acid. Here we propose oxidation of a 1° alcohol:



(d) The 1° alcohol, in turn, can be made from a Grignard reagent and formaldehyde:



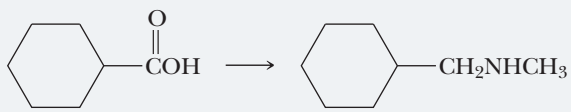
(e) In this manner, the alkene can be arrived at retrosynthetically:



EXAMPLE 14.7

Show how to bring about each conversion:

(a) C_6H_5COH (O) $\longrightarrow$ $C_6H_5CH_2$—N

(b) 

STRATEGY

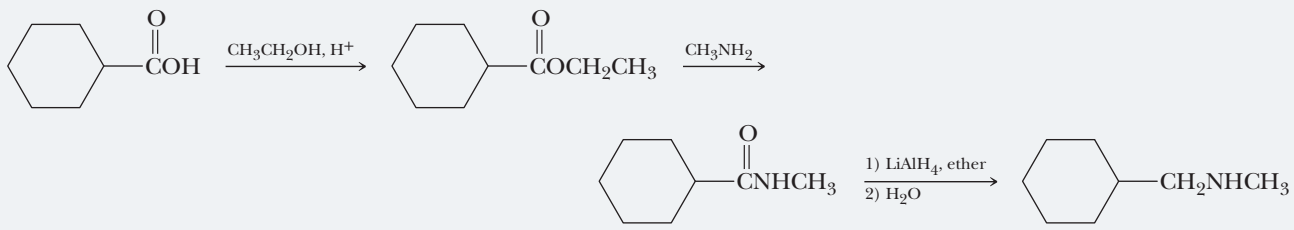
The key in each part is to convert the carboxylic acid to an amide (Section 14.5D) and then reduce the amide with $LiAlH_4$ (Section 14.8B).

SOLUTION

Each amide can be prepared by treating the carboxylic acid with $SOCl_2$ to form the acid chloride (Section 13.7) and then treating the acid chloride with an amine (Section 14.5A). Alternatively, the carboxylic acid can be converted to an ester by Fischer esterification (Section 13.6) and the ester treated with an amine to give the amide. Solution (a) uses the acid chloride route, solution (b) the ester route:

(a) $C_6H_5COH \xrightarrow{SOCl_2} C_6H_5CCl \xrightarrow{HN} C_6H_5C{-}N \xrightarrow[2)\ H_2O]{1)\ LiAlH_4,\ ether} C_6H_5CH_2{-}N$

(b)

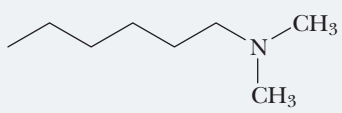


See problems 14.27, 14.29, 14.31, 14.32, 14.39, 14.46

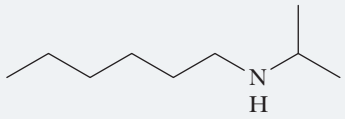
PROBLEM 14.7

Show how to convert hexanoic acid to each amine in good yield:

(a)



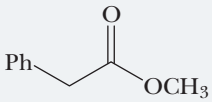
(b)



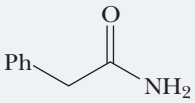
EXAMPLE 14.8

Show how to convert phenylacetic acid to these compounds:

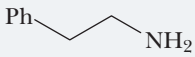
(a)



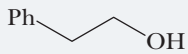
(b)



(c)



(d)

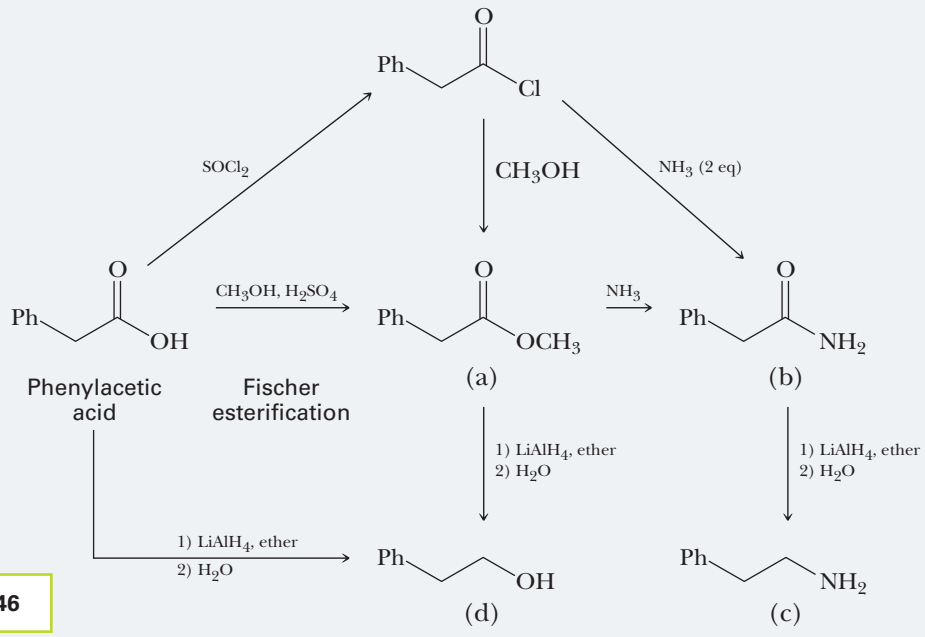


STRATEGY

Decide whether the functional group interconversion can be done in one step. If not, try to determine what functional group can be converted to the targeted group. For example, a carboxyl group cannot be converted directly to an amine. However, an amide can be converted to an amine. Therefore, one only needs to convert the carboxyl group into an amide to eventually be able to produce the amine.

SOLUTION

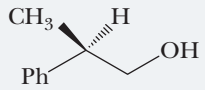
Prepare methyl ester (a) by Fischer esterification (Section 13.6) of phenylacetic acid with methanol. Then treat this ester with ammonia to prepare amide (b). Alternatively, treat phenylacetic acid with thionyl chloride (Section 13.7) to give an acid chloride, and then treat the acid chloride with two equivalents of ammonia to give amide (b). Reduction of amide (b) by $LiAlH_4$ gives the 1° amine (c). Similar reduction of either phenylacetic acid or ester (a) gives 1° alcohol (d):



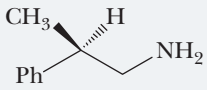
See problem 14.46

PROBLEM 14.8

Show how to convert (*R*)-2-phenylpropanoic acid to these compounds:

(a) 

(*R*)-2-Phenyl-1-propanol

(b) 

(*R*)-2-Phenyl-1-propanamine

SUMMARY OF KEY QUESTIONS

14.1 What Are Some Derivatives of Carboxylic Acids, and How Are They Named?

- The functional group of an **acid halide** is an acyl group bonded to a halogen.
- Acid halides are named by changing the suffix *-ic acid* in the name of the parent carboxylic acid to *-yl halide*.
- The functional group of a **carboxylic anhydride** is two acyl groups bonded to an oxygen.
- Symmetrical anhydrides are named by changing the suffix *acid* in the name of the parent carboxylic acid to *anhydride*.
- The functional group of a **carboxylic ester** is an acyl group bonded to —OR or —OAr.
- An ester is named by giving the name of the alkyl or aryl group bonded to oxygen first, followed by the name of the acid, in which the suffix *-ic acid* is replaced by the suffix *-ate*.
- A cyclic ester is given the name **lactone**.
- The functional group of an **amide** is an acyl group bonded to a trivalent nitrogen.
- Amides are named by dropping the suffix *-oic acid* from the IUPAC name of the parent acid, or *-ic acid* from its common name, and adding *-amide*.
- A cyclic amide is given the name **lactam**.

14.2 What Are the Characteristic Reactions of Carboxylic Acid Derivatives?

- A common reaction theme of functional derivatives of carboxylic acids is **nucleophilic acyl addition** to the carbonyl carbon to form a **tetrahedral carbonyl addition intermediate**, which then collapses to regenerate the carbonyl group. The result is **nucleophilic acyl substitution**.

14.3 What Is Hydrolysis?

- **Hydrolysis** is a chemical process whereby a bond (or bonds) in a molecule is broken by its reaction with water.
- Hydrolysis of a carboxylic acid derivative results in a carboxylic acid.

14.4 How Do Carboxylic Acid Derivatives React with Alcohols?

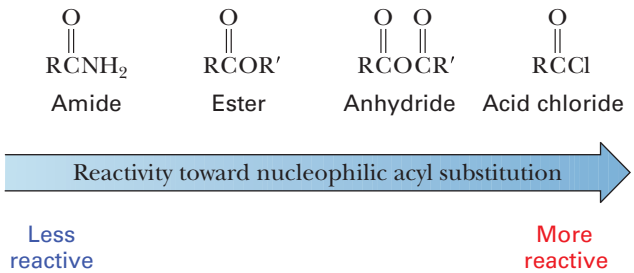
- Carboxylic acid derivatives (except for amides) react with alcohols to give esters.
- The reaction conditions required (i.e., neutral, acidic, or basic) depend on the type of derivative.

14.5 How Do Carboxylic Acid Derivatives React with Ammonia and Amines?

- Carboxylic acid derivatives (except for amides) react with ammonia and amines to give amides.

14.6 How Can Functional Derivatives of Carboxylic Acids Be Interconverted?

- Listed in order of increasing reactivity toward nucleophilic acyl substitution, these functional derivatives are:



- Any more reactive functional derivative can be directly converted to any less reactive functional derivative by reaction with an appropriate oxygen or nitrogen nucleophile.

14.7 How Do Esters React with Grignard Reagents?

- Reaction of an ester with a Grignard reagent involves the formation of two successive tetrahedral carbonyl addition compounds. The result of the overall reaction is an alcohol containing the two identical alkyl groups from the Grignard reagent.

14.8 How Are Derivatives of Carboxylic Acids Reduced?

- Derivatives of carboxylic acids are resistant to reduction by $NaBH_4$. Therefore, ketones and aldehydes can be selectively reduced in the presence of a carboxylic acid derivative.
- Derivatives of carboxylic acids are resistant to catalytic hydrogenation by H_2/M. Therefore, C—C double and triple bonds can be selectively reduced in the presence of a carboxylic acid derivative.
- $LiAlH_4$ reduces the carboxyl group of acid halides, acid anhydrides, and esters to a 1° alcohol group.
- $LiAlH_4$ reduces amides to amines.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. The stronger the base, the better the leaving group. (14.2)
2. Anhydrides can contain C—O double bonds or P—O double bonds. (14.1)
3. Acid anhydrides react with ammonia and amines without the need for acid or base. (14.5)
4. Derivatives of carboxylic acids are reduced by H_2/M. (14.8)
5. Aldehydes and ketones undergo nucleophilic acyl substitution reactions, while derivatives of carboxylic acids undergo nucleophilic addition reactions. (14.2)
6. Esters react with ammonia and amines without the need for acid or base. (14.5)
7. An acyl group is a carbonyl bonded to an alkyl (R) group. (14.1)
8. Hydrolysis is the loss of water from a molecule. (14.3)
9. Esters react with water without the need for acid or base. (14.4)
10. Acid anhydrides react with water without the need for acid or base. (14.3)
11. An acid halide can be converted to an amide in one step. (14.6)
12. An ester can be converted to an acid halide in one step. (14.6)
13. In the hydrolysis of an ester with base, hydroxide ion is a catalyst. (14.3)
14. Derivatives of carboxylic acids are reduced by $NaBH_4$. (14.8)
15. Acid anhydrides react with alcohols without the need for acid or base. (14.4)
16. Acid halides react with water without the need for acid or base. (14.3)
17. An ester of formic acid reacts with Grignard reagents to form a 3° alcohol. (14.7)
18. Acid halides react with ammonia and amines without the need for acid or base. (14.5)
19. A cyclic amide is called a lactone. (14.1)
20. The reactivity of a carboxylic acid derivative is dependent on the stability of its leaving group. (14.2)
21. Amides react with ammonia and amines without the need for acid or base. (14.5)
22. An amide can be converted to an ester in one step. (14.6)
23. Amides react with water without the need for acid or base. (14.3)
24. Esters react with alcohols without the need for acid or base. (14.3)
25. Amides react with alcohols under acidic or basic conditions. (14.4)
26. Esters other than formic acid esters react with Grignards to form ketones. (14.7)
27. Acid halides react with alcohols without the need for acid or base. (14.4)
28. An —OR group attached to a P—O double bond is known as an ester. (14.1)

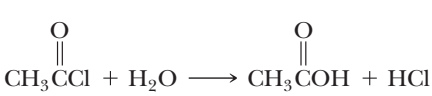
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) F (2) T (3) T (4) F (5) F (6) T (7) T (8) F (9) F (10) T (11) T (12) F (13) F (14) F (15) T (16) T (17) F (18) T (19) F (20) T (21) F (22) F (23) F (24) F (25) F (26) F (27) T (28) T

KEY REACTIONS

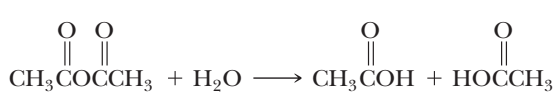
1. Hydrolysis of an Acid Chloride (Section 14.3A)

Low-molecular-weight acid chlorides react vigorously with water; higher-molecular-weight acid chlorides react less rapidly:



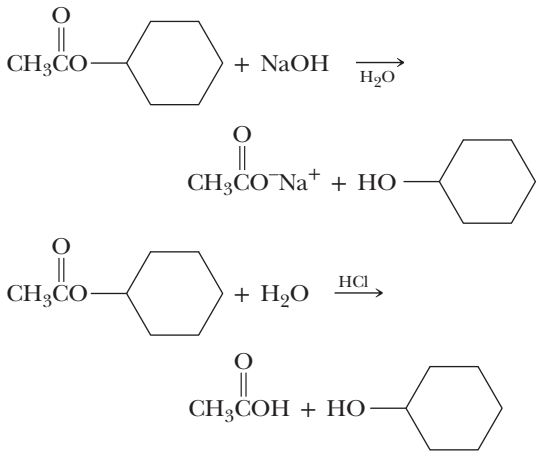
2. Hydrolysis of an Acid Anhydride (Section 14.3B)

Low-molecular-weight acid anhydrides react readily with water; higher-molecular-weight acid anhydrides react less rapidly:



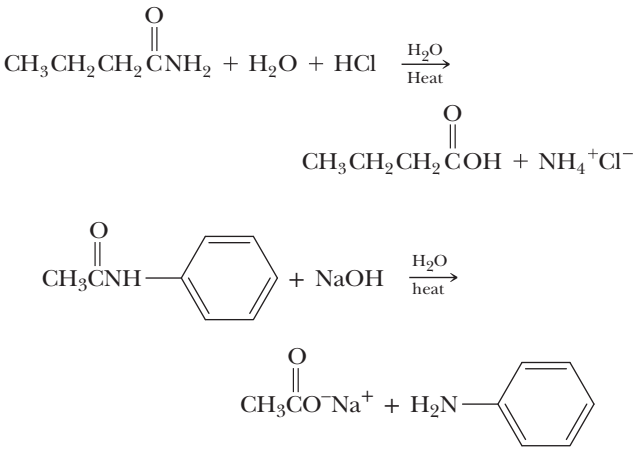
3. Hydrolysis of an Ester (Section 14.3C)

Esters are hydrolyzed only in the presence of base or acid; base is required in an equimolar amount, acid is a catalyst:



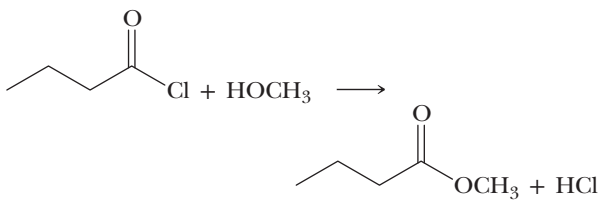
4. Hydrolysis of an Amide (Section 14.3D)

Either acid or base is required in an amount equivalent to that of the amide:



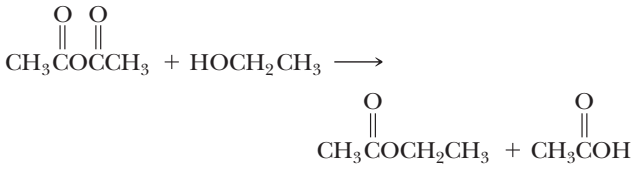
5. Reaction of an Acid Chloride with an Alcohol (Section 14.4A)

Treatment of an acid chloride with an alcohol gives an ester and HCl:



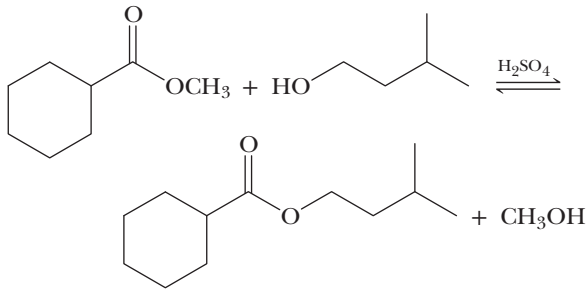
6. Reaction of an Acid Anhydride with an Alcohol (Section 14.4B)

Treatment of an acid anhydride with an alcohol gives an ester and a carboxylic acid:



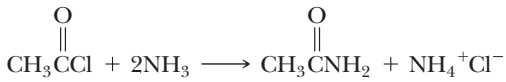
7. Reaction of an Ester with an Alcohol (Section 14.4C)

Treatment of an ester with an alcohol in the presence of an acid catalyst results in transesterification—that is, the replacement of one —OR group by a different —OR group:



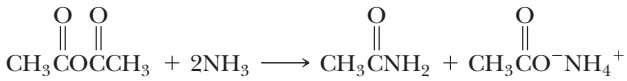
8. Reaction of an Acid Chloride with Ammonia or an Amine (Section 14.5A)

Reaction requires two moles of ammonia or amine—one mole to form the amide and one mole to neutralize the HCl by-product:



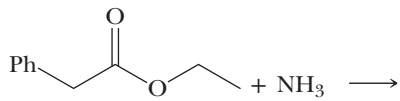
9. Reaction of an Acid Anhydride with Ammonia or an Amine (Section 14.5B)

Reaction requires two moles of ammonia or amine—one mole to form the amide and one mole to neutralize the carboxylic acid by-product:

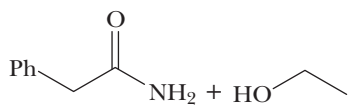


10. Reaction of an Ester with Ammonia or an Amine (Section 14.5C)

Treatment of an ester with ammonia, a 1° amine, or a 2° amine gives an amide:



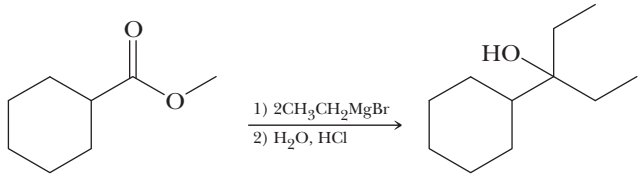
Ethyl phenylacetate



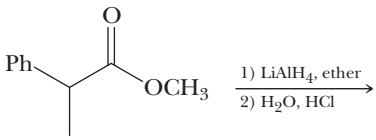
Phenylacetamide Ethanol

11. Reaction of an Ester with a Grignard Reagent (Section 14.7)

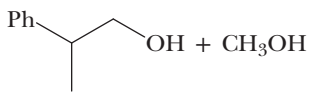
Treating a formic ester with a Grignard reagent, followed by hydrolysis, gives a 2° alcohol, whereas treating any other ester with a Grignard reagent gives a 3° alcohol:



12. Reduction of an Ester (Section 14.8A)
Reduction by lithium aluminum hydride gives two alcohols:

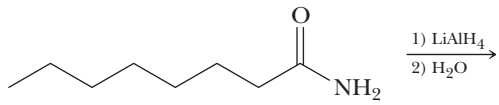


Methyl 2-phenylpropanoate

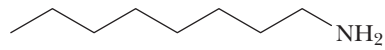


2-Phenyl-1-propanol Methanol

13. Reduction of an Amide (Section 14.8B)
Reduction by lithium aluminum hydride gives an amine:



Octanamide



1-Octanamine

PROBLEMS

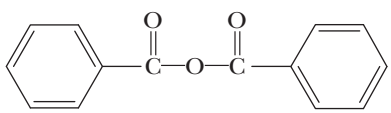
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

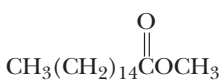
SECTION 14.1 Structure and Nomenclature

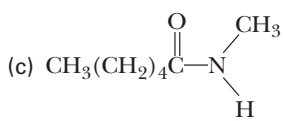
14.9 Draw a structural formula for each compound: **(See Example 14.1)**

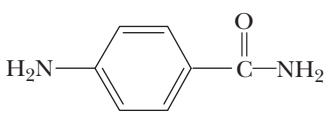
(a) Dimethyl carbonate
(b) *p*-Nitrobenzamide
(c) Octanoyl chloride
(d) Diethyl oxalate
(e) Ethyl *cis*-2-pentenoate
(f) Butanoic anhydride
(g) Dodecanamide
(h) Ethyl 3-hydroxybutanoate
(i) Ethyl benzoate
(j) Benzoyl chloride
(k) *N*-Ethylpentanamide
(l) 5-Methylhexanoyl chloride

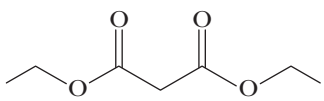
14.10 Write the IUPAC name for each compound: **(See Example 14.1)**

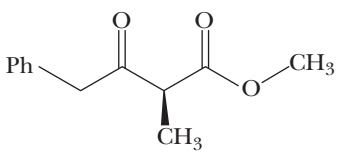
(a) 

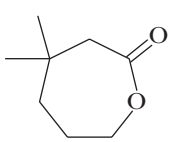
(b) 

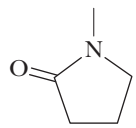
(c) 

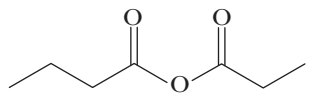
(d) 

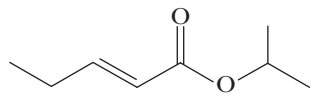
(e) 

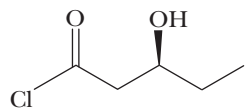
(f) 

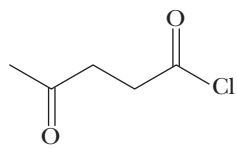
(g) 

(h) 

(i) 

(j) 

(k) 

(l) 

***14.11** When oil from the head of a sperm whale is cooled, spermaceti, a translucent wax with a white, pearly luster, crystallizes from the mixture. Spermaceti, which makes up 11% of whale oil, is composed mainly of hexadecyl hexadecanoate (cetyl palmitate). At one time, spermaceti was widely used in the making of cosmetics, fragrant soaps, and candles. Draw a structural formula of cetyl palmitate. **(See Example 14.1)**

Wolfgang Poelzer/Waterframe RM/ Getty Images, Inc.

Sperm whale, *Physterer macrocephalus*, diving, Kaikoura, NZ.

Physical Properties

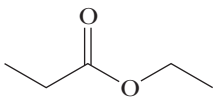
14.12 Acetic acid and methyl formate are constitutional isomers. Both are liquids at room temperature, one with a boiling point of 32 °C, the other with a boiling point of 118 °C. Which of the two has the higher boiling point?

14.13 Butanoic acid (88.11 g/mol) has a boiling point of 162 °C, whereas its propyl ester (130.18 g/mol) has a boiling point of 142 °C. Account for the fact that the boiling point of butanoic acid is higher than that of its propyl ester, even though butanoic acid has a lower molecular weight.

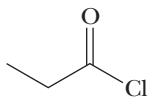
14.14 The constitutional isomers pentanoic acid and methyl butanoate are both slightly soluble in water. One of these compounds has a solubility of 1.5 g/100 ml (25 °C), while the other has a solubility of 4.97 g/100 ml (25 °C). Assign the solubilities to each compound and account for the differences.

SECTIONS 14.2–14.8 Reactions

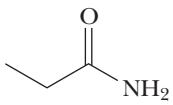
14.15 Arrange these compounds in order of increasing reactivity toward nucleophilic acyl substitution:



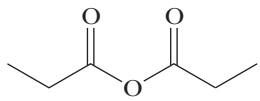
(1)



(2)



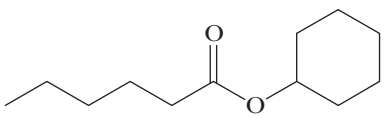
(3)



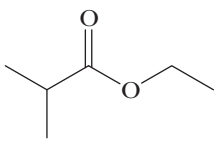
(4)

14.16 A carboxylic acid can be converted to an ester by Fischer esterification. Show how to synthesize each ester from a carboxylic acid and an alcohol by Fischer esterification: **(See Example 14.4)**

(a)



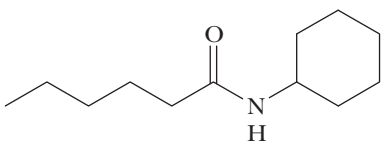
(b)



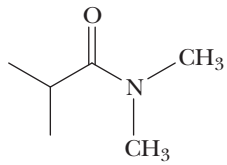
14.17 A carboxylic acid can also be converted to an ester in two reactions by first converting the carboxylic acid to its acid chloride and then treating the acid chloride with an alcohol. Show how to prepare each ester in Problem 14.16 from a carboxylic acid and an alcohol by this two-step scheme. **(See Example 14.4)**

14.18 Show how to prepare these amides by reaction of an acid chloride with ammonia or an amine: **(See Example 14.5)**

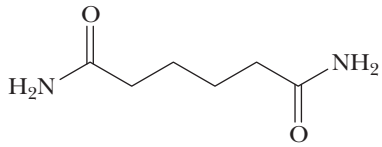
(a)



(b)

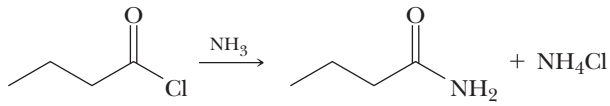


(c)

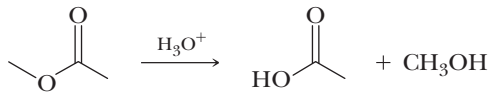


14.19 Balance and write a mechanism for each of the following reactions. **(See Examples 14.2, 14.4, 14.5)**

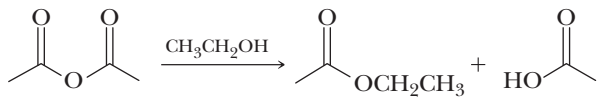
(a)



(b)



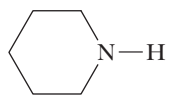
(c)



14.20 What product is formed when benzoyl chloride is treated with these reagents? **(See Examples 14.2, 14.4, 14.5)**

(a) C_6H_6, $AlCl_3$ (b) $CH_3CH_2CH_2CH_2OH$

(c) $CH_3CH_2CH_2CH_2SH$ (d) $CH_3CH_2CH_2CH_2NH_2$ (2 equivalents)

(e) H_2O (f)  (2 equivalents)

14.21 Write the product(s) of the treatment of propanoic anhydride with each reagent: **(See Examples 14.4, 14.5)**

(a) Ethanol (1 equivalent)

(b) Ammonia (2 equivalents)

14.22 Write the product of the treatment of benzoic anhydride with each reagent: **(See Examples 14.4, 14.5)**

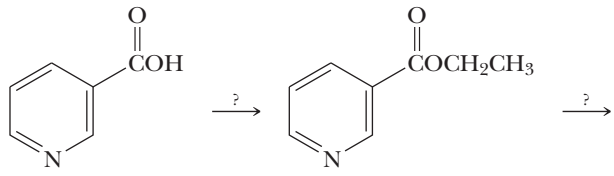
(a) Ethanol (1 equivalent)

(b) Ammonia (2 equivalents)

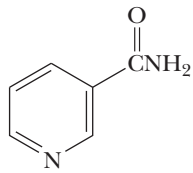
***14.23** The analgesic phenacetin is synthesized by treating 4-ethoxyaniline with acetic anhydride. Write an equation for the formation of phenacetin.

***14.24** The analgesic acetaminophen is synthesized by treating 4-aminophenol with one equivalent of acetic anhydride. Write an equation for the formation of acetaminophen. (*Hint*: Remember from Section 7.5A that an —NH_2 group is a better nucleophile than an —OH group.) **(See Example 14.5)**

***14.25** Nicotinic acid, more commonly named niacin, is one of the B vitamins. Show how nicotinic acid can be converted to ethyl nicotinate and then to nicotinamide: **(See Example 14.5)**

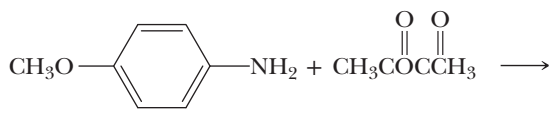


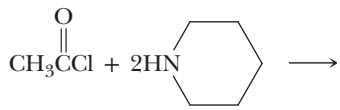
Nicotinic acid (Niacin) Ethyl nicotinate

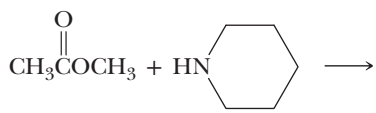


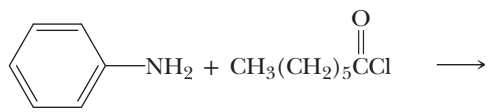
Nicotinamide

14.26 Complete these reactions: **(See Example 14.5)**

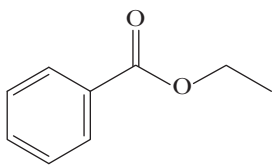
(a) 

(b) 

(c) 

(d) 

14.27 What product is formed when ethyl benzoate is treated with these reagents? **(See Example 14.7)**



Ethyl benzoate

(a) H_2O, NaOH, heat

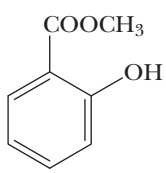
(b) $LiAlH_4$, then H_2O

(c) H_2O, H_2SO_4, heat

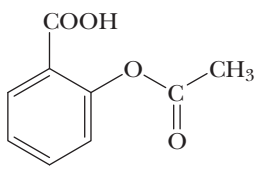
(d) $CH_3CH_2CH_2CH_2NH_2$

(e) C_6H_5MgBr (2 moles) and then H_2O/HCl

***14.28** Show how to convert 2-hydroxybenzoic acid (salicylic acid) to these compounds: **(See Example 14.4)**

(a) 

Methyl salicylate (Oil of wintergreen)

(b) 

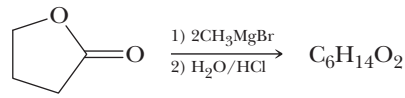
Acetyl salicylic acid (Aspirin)

14.29 What product is formed when benzamide is treated with these reagents? **(See Examples 14.3, 14.7)**

(a) H_2O, HCl, heat (b) NaOH, H_2O, heat

(c) $LiAlH_4$/ether, then H_2O

14.30 Treating γ-butyrolactone with two equivalents of methylmagnesium bromide, followed by hydrolysis in aqueous acid, gives a compound with the molecular formula $C_6H_{14}O_2$: **(See Example 14.6)**



Propose a structural formula for this compound.

14.31 Show the product of treating γ-butyrolactone with each reagent: **(See Examples 14.2, 14.5, 14.7)**

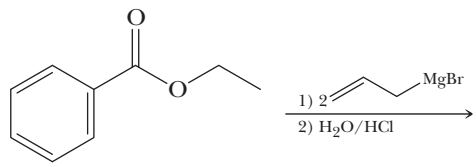
(a) NH_3 (b) $LiAlH_4$/ether, then H_2O (c) NaOH, H_2O, heat

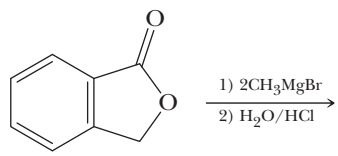
14.32 Show the product of treating *N*-methyl-γ-butyrolactam with each reagent: **(See Examples 14.3, 14.7)**

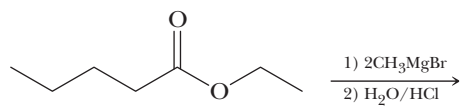
(a) H_2O, HCl, heat (b) NaOH, H_2O, heat

(c) $LiAlH_4$/ether, then H_2O

14.33 Complete these reactions: **(See Example 14.6)**

(a) 

(b) 

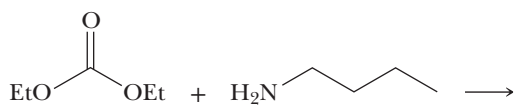
(c) 

14.34 What combination of ester and Grignard reagent can be used to prepare each alcohol? **(See Example 14.6)**

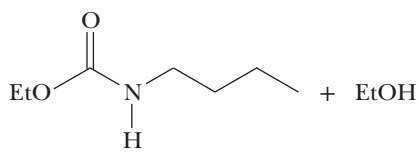
(a) 2-Methyl-2-butanol (b) 3-Phenyl-3-pentanol

(c) 1,1-Diphenylethanol

14.35 Reaction of a 1° or 2° amine with diethyl carbonate under controlled conditions gives a carbamic ester: **(See Example 14.5)**



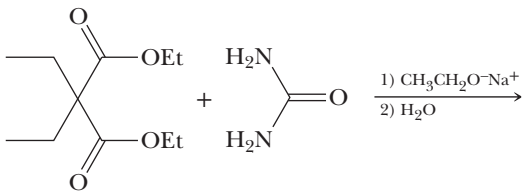
Diethyl carbonate 1-Butanamine (Butylamine)



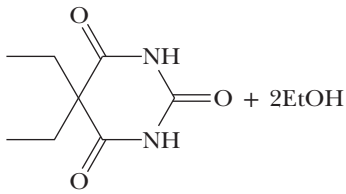
A carbamic ester

Propose a mechanism for this reaction.

***14.36** Barbiturates are prepared by treating diethyl malonate or a derivative of diethyl malonate with urea in the presence of sodium ethoxide as a catalyst. Following is an equation for the preparation of barbital from diethyl 2,2-diethylmalonate and urea (barbital, a long-duration hypnotic and sedative, is prescribed under a dozen or more trade names):



Diethyl 2,2-diethylmalonate — Urea



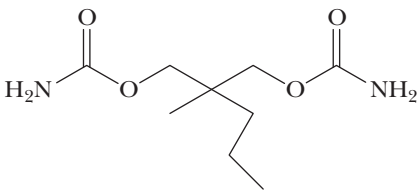
5,5-Diethylbarbituric acid (Barbital)

(a) Propose a mechanism for this reaction.

(b) The pK_a of barbital is 7.4. Which is the most acidic hydrogen in this molecule, and how do you account for its acidity?

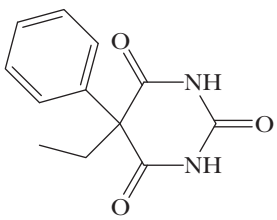
***14.37** Name and draw structural formulas for the products of the complete hydrolysis of meprobamate and phenobarbital in hot aqueous acid. Meprobamate is a tranquilizer, now replaced by benzodiazepines, that was once prescribed under 58 different trade names. Phenobarbital is a long-acting sedative, hypnotic, and anticonvulsant. [*Hint*: Remember that, when heated, β-dicarboxylic acids and β-ketoacids undergo decarboxylation (Section 13.8B).]

(a)



Meprobamate

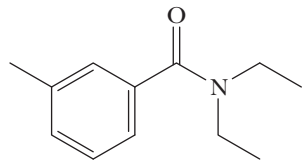
(b)



Phenobarbital

Synthesis

***14.38** The active ingredient in several common insect repellents *N,N*-Diethyl-*m*-toluamide (Deet) is synthesized from 3-methylbenzoic acid (*m*-toluic acid) and diethylamine:

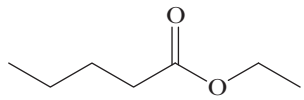


N,N-Diethyl-*m*-toluamide (Deet)

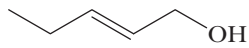
Show how this synthesis can be accomplished.

14.39 Show how to convert ethyl 2-pentenoate into these compounds: **(See Example 14.7)**

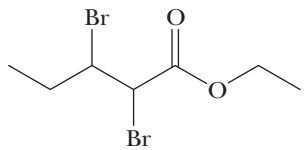
(a)



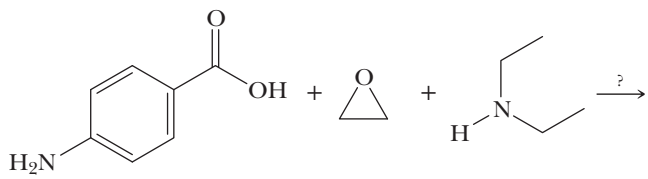
(b)



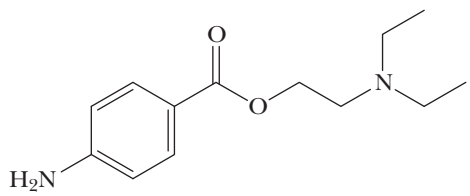
(c)



***14.40** Procaine (whose hydrochloride is marketed as Novocaine®) was one of the first local anesthetics for infiltration and regional anesthesia. Show how to synthesize procaine, using the three reagents shown as the sources of carbon atoms:



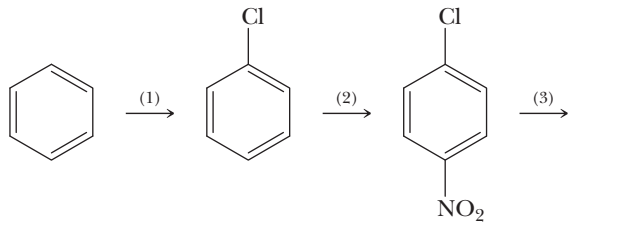
4-Aminobenzoic acid — Ethylene oxide — Diethylamine

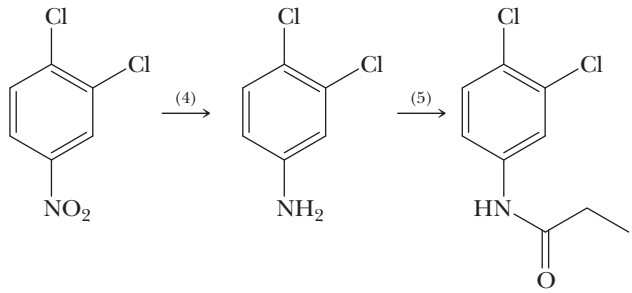


Procaine

14.41 There are two nitrogen atoms in procaine. Which of the two is the stronger base? Draw the structural formula for the salt that is formed when procaine is treated with 1 mole of aqueous HCl.

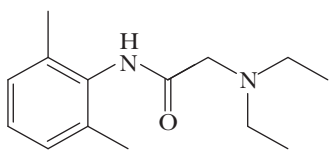
***14.42** Starting materials for the synthesis of the herbicide propanil, a weed killer used in rice paddies, are benzene and propanoic acid. Show reagents to bring about this synthesis:



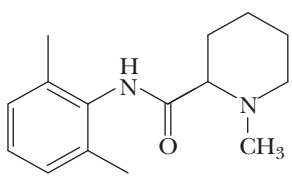


Propanil

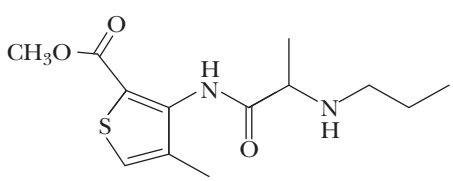
***14.43** Following are structural formulas for three local anesthetics: Lidocaine was introduced in 1948 and is one of the most widely used local anesthetics for infiltration and regional anesthesia. Its hydrochloride is marketed under the name Xylocaine®. Mepivacaine (its hydrochloride is marketed as Carbocaine®) is faster and somewhat longer in duration than lidocaine. Articaine is the most widely used local anesthetic in Europe and contains two carboxylic acid derivative groups.



Lidocaine
(Xylocaine®)



Mepivocaine
(Carbocaine®)



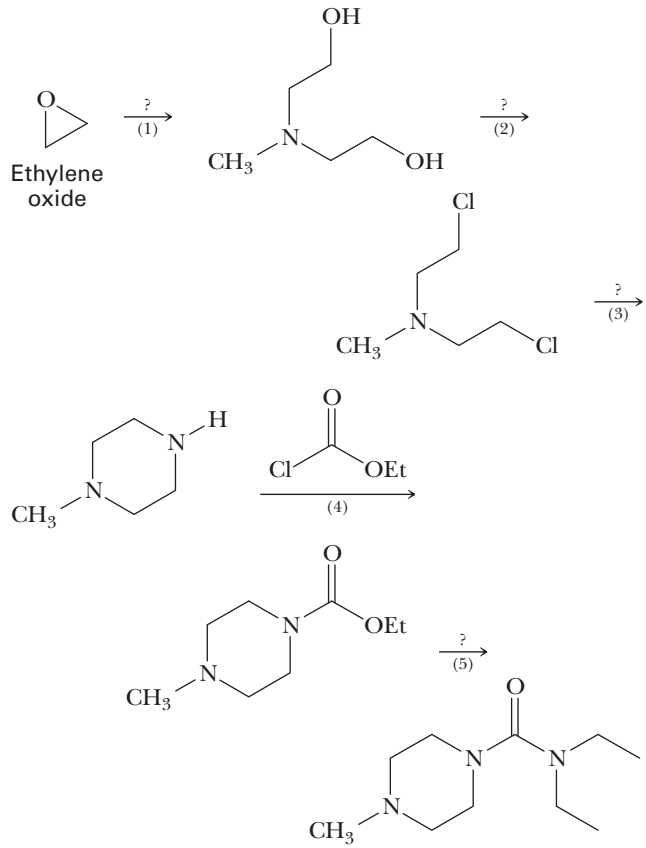
Articaine

(a) Propose a synthesis of lidocaine from 2,6-dimethylaniline, chloroacetyl chloride ($ClCH_2COCl$), and diethylamine.

(b) What amine and acid chloride can be reacted to give mepivacaine?

(c) Draw the products of acid-catalyzed hydrolysis of both acid derivative groups in articaine.

***14.44** Following is the outline of a five-step synthesis for the anthelmintic (against worms) diethylcarbamazine:



Diethylcarbamazine

Diethylcarbamazine is used chiefly against nematodes, small cylindrical or slender threadlike worms such as the common roundworm, which are parasitic in animals and plants.

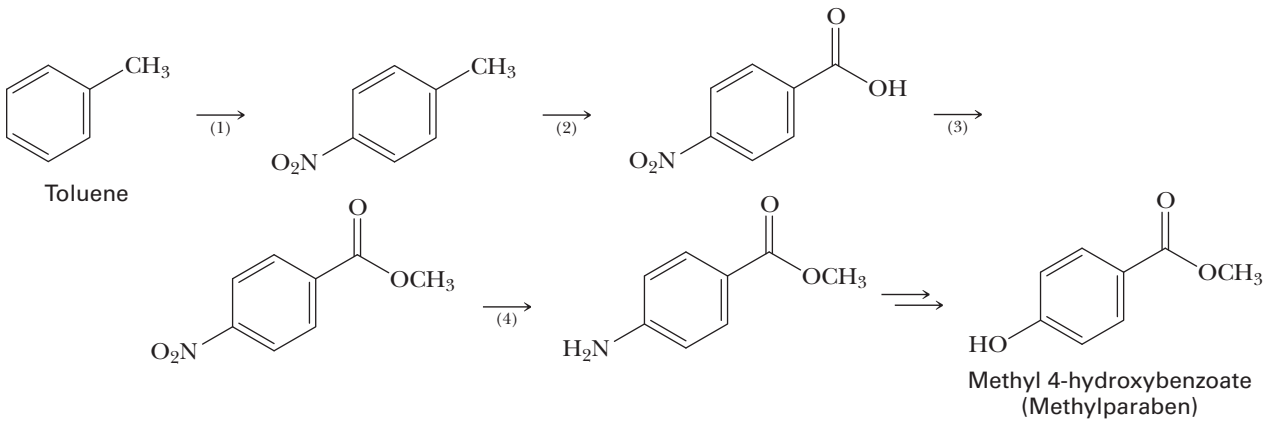
(a) Propose a reagent for Step 1. Which mechanism is more likely for this step, S_N1 or S_N2? Explain.

(b) Propose a reagent for Step 2.

(c) Propose a reagent for Step 3.

(d) Ethyl chloroformate, the reagent for Step 4, is both an acid chloride and an ester. Account for the fact that Cl, rather than OCH_2CH_3, is displaced from this reagent.

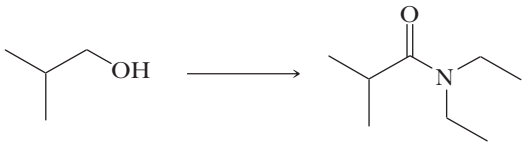
***14.45** Following is an outline of a multi-step synthesis for methylparaben, a compound widely used as a preservative in foods:

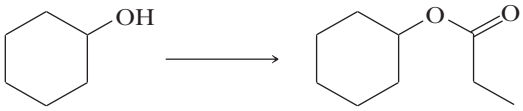


Propose reagents for Steps 1–4.

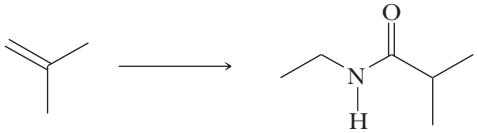
CHEMICAL TRANSFORMATIONS

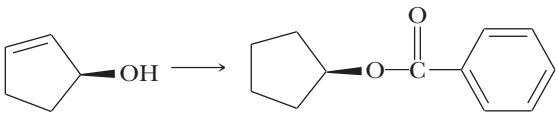
14.46 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note*: Some will require more than one step. **(See Examples 14.7, 14.8)**

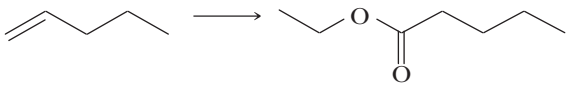
(a) 

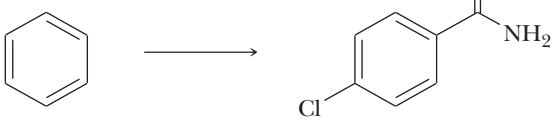
(b) 

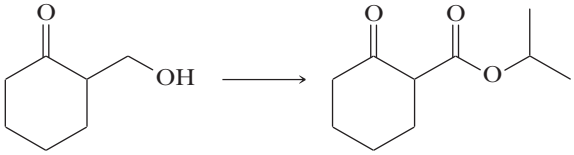
(c) 

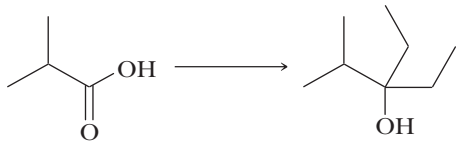
(d) 

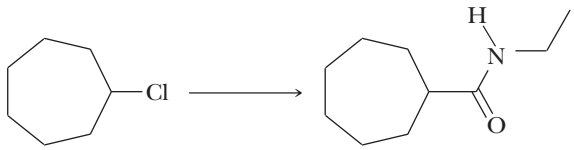
(e) 

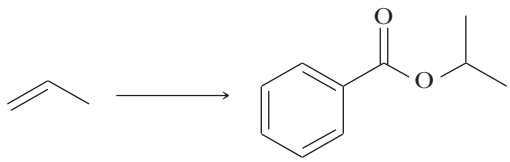
(f) 

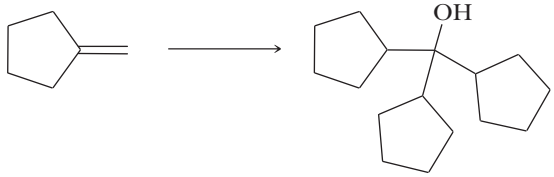
(g) 

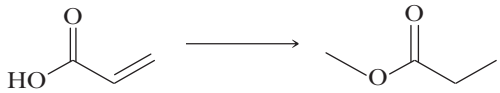
(h) 

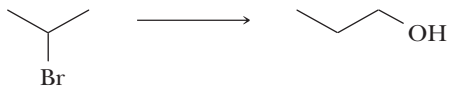
(i) 

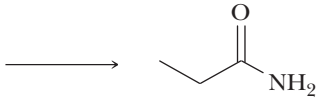
(j) 

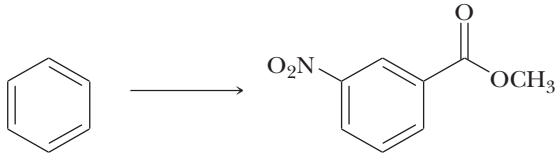
(k) 

(l) 

(m) 

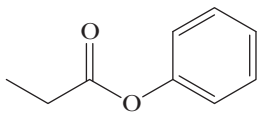
(n) 

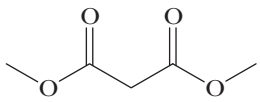
(o) $CH_3—C\equiv C—H$ 

(p) 

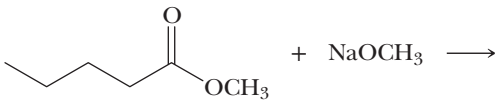
LOOKING AHEAD

14.47 Identify the most acidic proton in each of the following esters:

(a) 

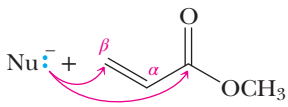
(b) 

14.48 Does a nucleophilic acyl substitution occur between the ester and the nucleophile shown?

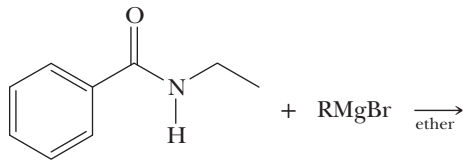


Propose an experiment that would verify your answer.

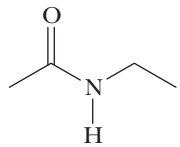
14.49 Explain why a nucleophile, Nu, attacks not only the carbonyl carbon, but also the β-carbon, as indicated in the following α,β-unsaturated ester:



14.50 Explain why a Grignard reagent will not undergo nucleophilic acyl substitution with the following amide:



14.51 At low temperatures, the following amide exhibits *cis–trans* isomerism, while at higher temperatures it does not:



Explain how this is possible.

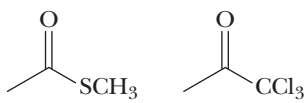
GROUP LEARNING ACTIVITIES

14.52 Following are two compounds that can also undergo nucleophilic acyl substitution. As a group:

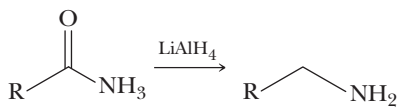
(a) Predict the product if each was treated with NaOH.

(b) Provide a mechanism for each reaction.

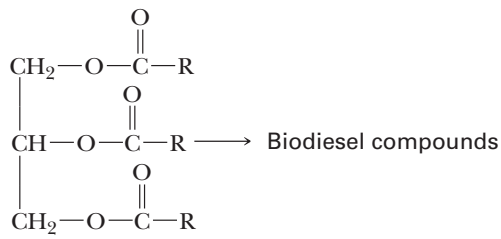
(c) Compare the leaving group ability of $^-SCH_3$ with that of $^-OCH_3$ and of $^-CCl_3$ with that of $^-CH_3$.



14.53 The mechanism of the reduction of amides to amines by $LiAlH_4$ contains many steps. Work as a group to figure out this mechanism. *Hint*: The carbonyl oxygen is removed as $^-OAlH_2$.



14.54 Biodiesel is a type of fuel consisting of long chain methyl esters created from naturally obtained lipids (e.g., vegetable oils) which have the general structures shown below. Propose a reaction or series of reactions that will convert lipids to biodiesel.

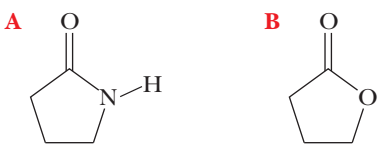


PUTTING IT TOGETHER

The following problems bring together concepts and material from Chapters 12–14. Although the focus may be on these chapters, the problems will also build upon concepts discussed throughout the text thus far.

Choose the best answer for each of the following questions.

1. Which of the following statements is true concerning the following two carboxylic acid derivatives?



(a) Only molecule **A** can be hydrolyzed.

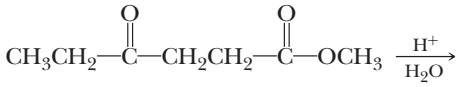
(b) Only molecule **B** can be hydrolyzed.

(c) Both molecules are hydrolyzable, but **A** will react more quickly than **B**.

(d) Both molecules are hydrolyzable, but **B** will react more quickly than **A**.

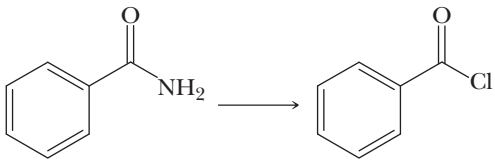
(e) **A** and **B** are hydrolyzed at roughly the same rate.

2. How many unique reaction products are formed from the following reaction?



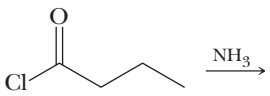
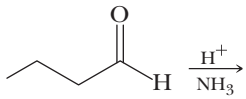
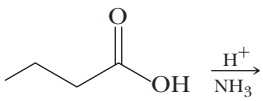
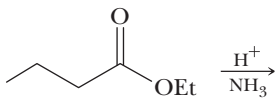
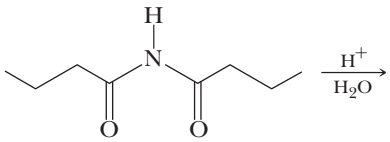
(a) one (b) two (c) three (d) four (e) five

3. What sequence of reagents will accomplish the following transformation?

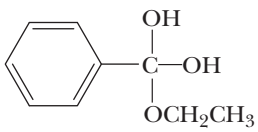
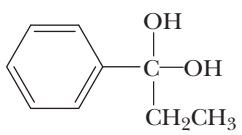
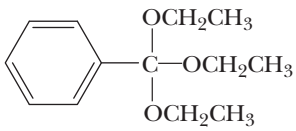
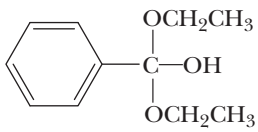
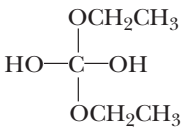


(a) 1) $SOCl_2$ (b) 1) H_2O_2, $SOCl_2$
(c) 1) H_2O_2, HCl (d) 1) H^+/H_2O_2 2) $SOCl_2$
(e) All of the above

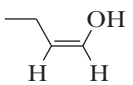
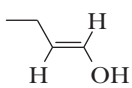
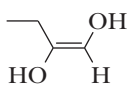
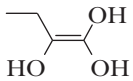
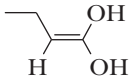
4. Which of the following reactions will not yield butanamide?

(a) 
(b) 
(c) 
(d) 
(e) 

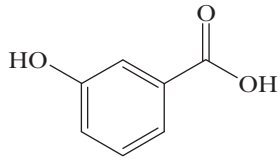
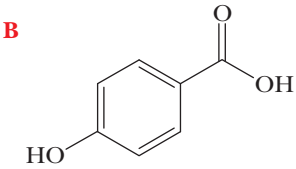
5. Which of the following is the tetrahedral carbonyl addition intermediate (TCAI) for the Fischer esterification of ethanol and benzoic acid?

(a) 
(b) 
(c) 
(d) 
(e) 

6. Which of the following is the enol intermediate in the decarboxylation of ethylpropanedioic acid?

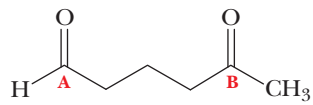
(a) 
(b) 
(c) 
(d) 
(e) 

7. Which of the following statements is true concerning the two carboxylic acids shown?

A 
B 

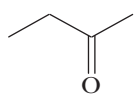
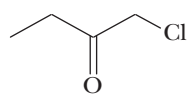
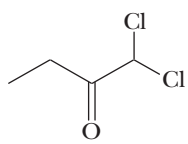
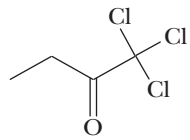
(a) **A** is more acidic than **B** because of an additional resonance effect.
(b) **B** is more acidic than **A** because of an additional resonance effect.
(c) Only the conjugate base of **A** experiences an inductive effect.
(d) Only the conjugate base of **B** experiences an inductive effect.
(e) None of the above.

8. What would be the expected outcome if one equivalent of a Grignard reagent were reacted with the molecule below?

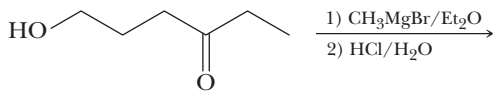


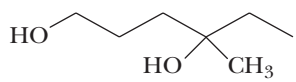
(a) 100% addition at carbonyl **A**.
(b) 100% addition at carbonyl **B**.
(c) Equal addition at both carbonyls.
(d) Greater distribution of addition at **A**.
(e) Greater distribution of addition at **B**.

9. Which of the following carbonyl carbons would be considered the most electrophilic?

(a) 
(b) 
(c) 
(d) 
(e) All are equally electrophilic.

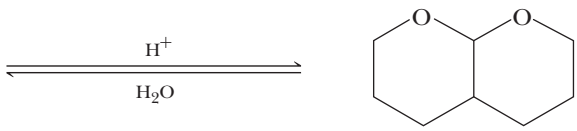
10. The following reaction will occur as shown:



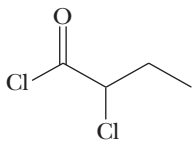


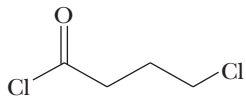
(a) True (b) False

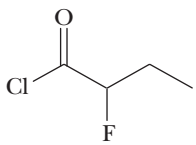
11. Provide a structure for the starting compound needed to produce the product shown. Then show the mechanism of its formation. Show all charges and lone pairs of electrons in your structures.

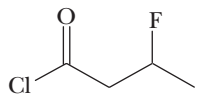


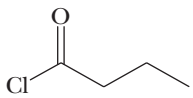
12. Rank the following from most to least reactive with EtOH. Provide a rationale for your ranking.

(a) 

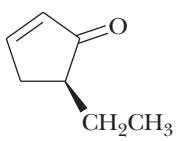
(b) 

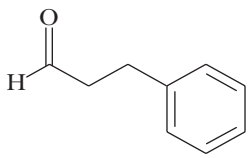
(c) 

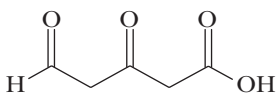
(d) 

(e) 

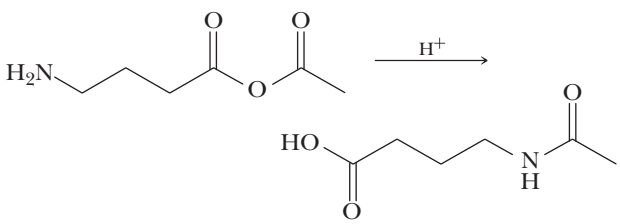
13. Provide IUPAC names for the following compounds.

(a) 

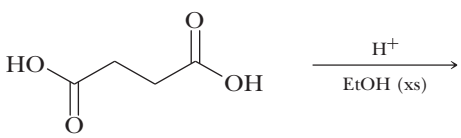
(b) 

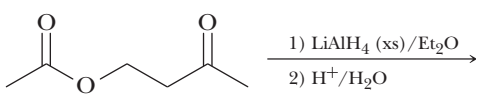
(c) 

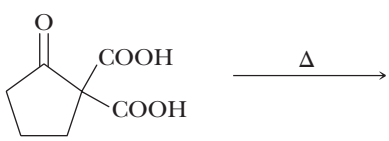
14. Provide a mechanism for the following reaction. Show all charges and lone pairs of electrons in your structures, as well as the structures of all intermediates.

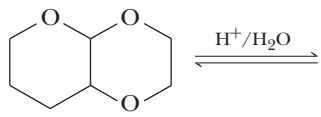


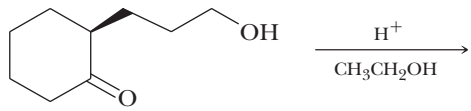
15. Predict the major product of each of the following reactions.

(a) 

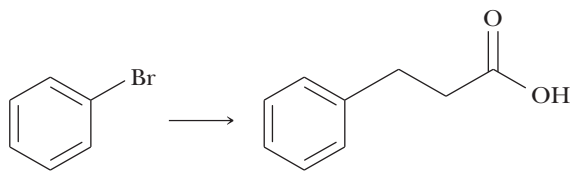
(b) 

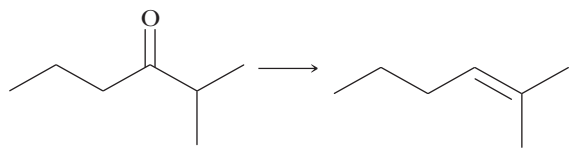
(c) 

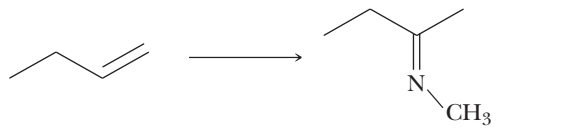
(d) 

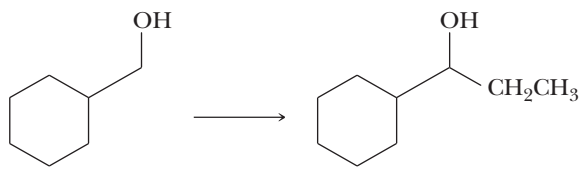
(e) 

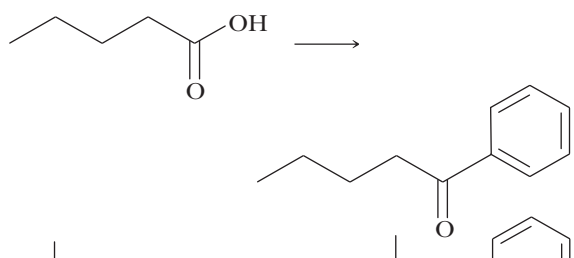
16. Complete the following chemical transformations.

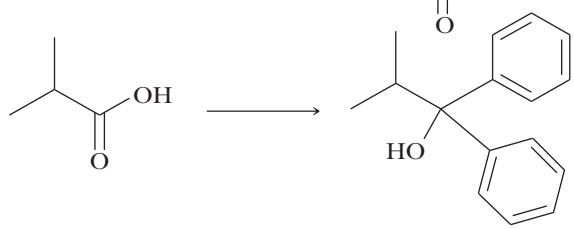
(a) 

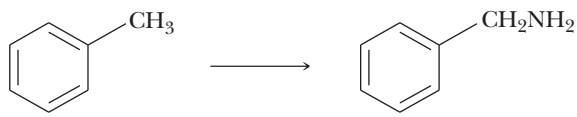
(b) 

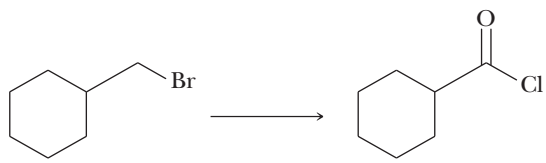
(c) 

(d) 

(e) 

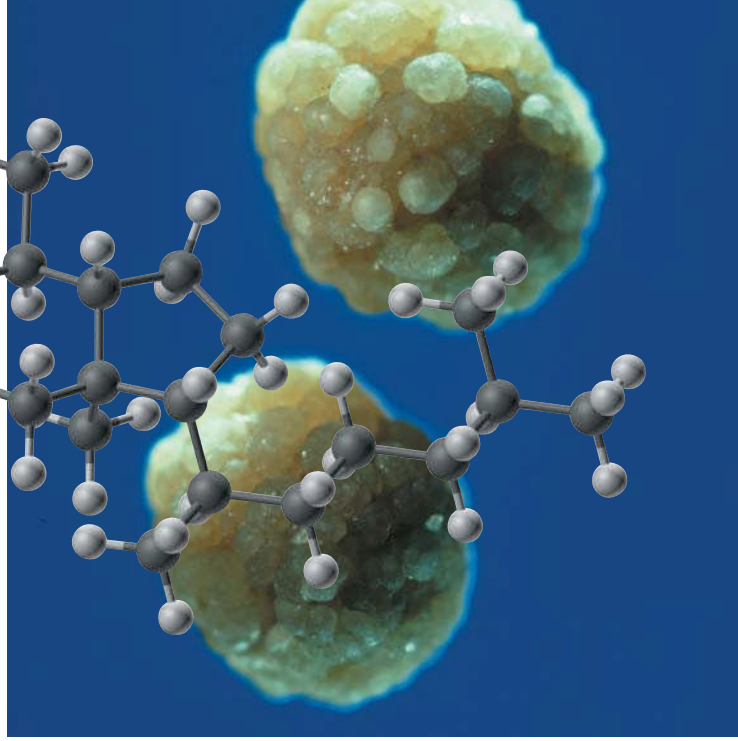
(f) 

(g) 

(h) 

Enolate Anions

15



Human gallstones are almost pure cholesterol; these two gallstones are about 0.5 cm in diameter. See Chemical Connections 15A. Inset: A model of cholesterol.

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KEY QUESTIONS

HOW TO

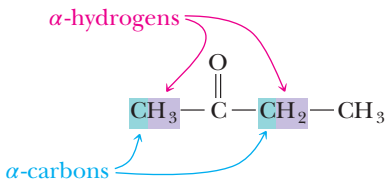
CHEMICAL CONNECTIONS

IN THIS CHAPTER, we continue our discussion of the chemistry of carbonyl compounds. In Chapters 12–14, we concentrated on the carbonyl group itself and on nucleophilic additions to it to form tetrahedral carbonyl addition compounds. In the current chapter, we expand on the chemistry of carbonyl-containing compounds and consider the acidity of α-hydrogens and the anions formed by their removal. The reactions presented here represent some of the most important reactions in organic chemistry because they involve the formation of carbon–carbon bonds, allowing the construction of larger molecules from smaller, readily available starting materials.

15.1 What Are Enolate Anions, and How Are They Formed?

A. Acidity of α-Hydrogens

A carbon atom adjacent to a carbonyl group is called an ***α*-carbon**, and a hydrogen atom bonded to it is called an ***α*-hydrogen**:



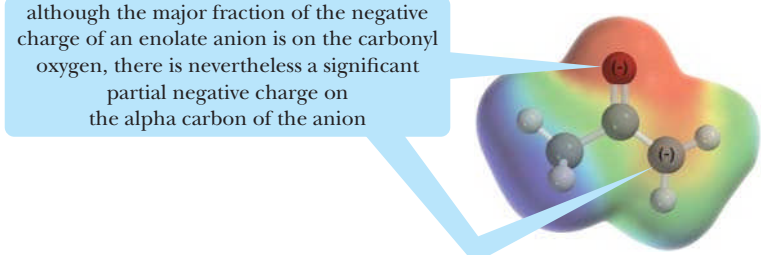
Because carbon and hydrogen have comparable electronegativities, a C—H bond normally has little polarity, and a hydrogen atom bonded to carbon shows very low acidity (Section 2.3). The situation is different, however, for hydrogens that are alpha to a carbonyl group. As Table 15.1 shows, α-hydrogens of aldehydes, ketones, and esters are considerably more acidic than alkane and alkene hydrogens, but less acidic than the hydroxyl hydrogen of alcohols. The table also shows that hydrogens that are alpha to two carbonyl groups—for example, in a β-ketoester and a β-diester—are even more acidic than alcohols.

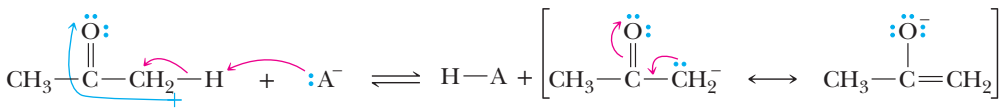
B. Enolate Anions

Carbonyl groups increase the acidity of their alpha hydrogens in two ways. First, the electron-withdrawing inductive effect of the carbonyl group weakens the bond to the alpha hydrogen and promotes its ionization. Second, the negative charge on the resulting **enolate anion** is delocalized by resonance, thus stabilizing it relative to the anion from an alkane or an alkene:

Enolate anion An anion formed by the removal of an α-hydrogen from a carbonyl-containing compound.

although the major fraction of the negative charge of an enolate anion is on the carbonyl oxygen, there is nevertheless a significant partial negative charge on the alpha carbon of the anion





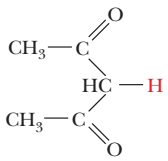
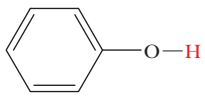
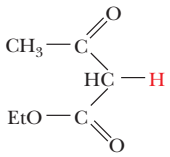
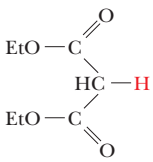
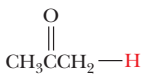
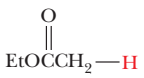
the electron-withdrawing inductive effect of the carbonyl weakens the C—H bond

resonance stabilizes the enolate anion

Recall that we used these same two factors in Section 2.5 to account for the greater acidity of carboxylic acids compared with alcohols.

Enolate anions can be formed either quantitatively or under equilibrium conditions. Use of a base that is much stronger than the ensuing enolate anion results in the quantitative removal of an α-hydrogen.

TABLE 15.1 The Acidity of Hydrogens Alpha to a Carbonyl Group Relative to Other Organic Hydrogens

Class of Compound	Example	pK_a
β-Diketone		9.5
Phenol		10
β-Ketoester (an acetoacetic ester)		10.7
β-Diester (a malonic ester)		13
Water	$HO-H$	15.7
Alcohol	CH_3CH_2O-H	16
Aldehyde or a ketone		20
Ester		22
Terminal alkyne	$R-C\equiv C-H$	25
Alkene	$CH_2=CH-H$	44
Alkane	CH_3CH_2-H	51

Increasing acidity

EXAMPLE 15.1

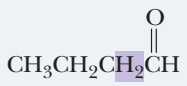
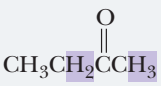
Identify the acidic α-hydrogens in each compound:
(a) Butanal **(b)** 2-Butanone

STRATEGY

Identify all carbon atoms bonded to a carbonyl group. These are the α-carbons. Any hydrogens bonded to these α-carbon atoms are α-hydrogens and are more acidic than typical alkane or alkene hydrogens.

SOLUTION

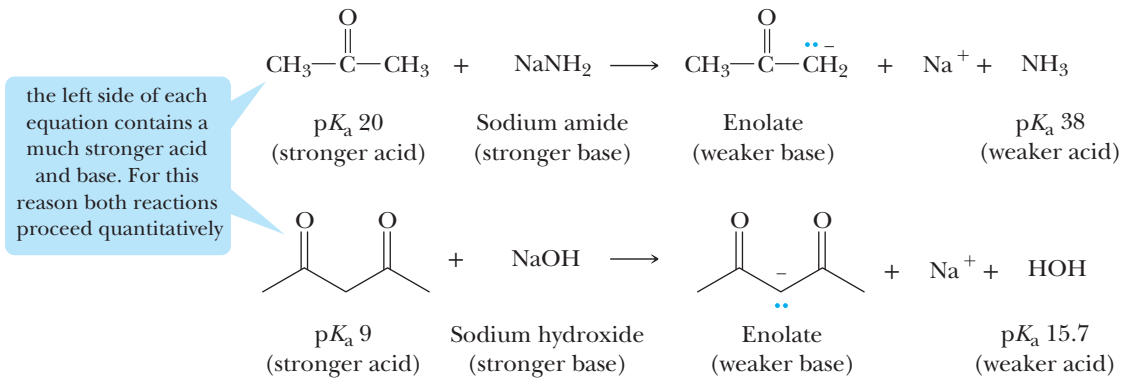
Butanal (a) has one set of acidic α-hydrogens, and 2-butanone (b) has two sets:

(a)  **(b)** 

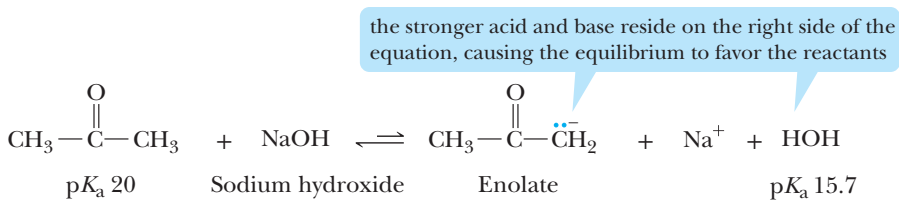
See problem 15.13

PROBLEM 15.1

Identify the acidic α-hydrogens in each compound:
(a) 2-Methylcyclohexanone **(b)** Acetophenone **(c)** 2,2-Diethylcyclohexanone



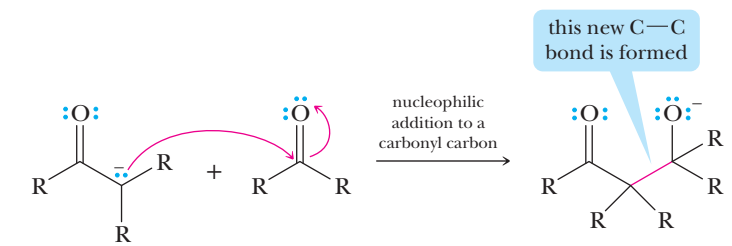
Use of a base that is weaker than the ensuing enolate anion results in an equilibrium in which the enolate exists in very small concentrations.



C. The Use of Enolate Anions to Form New C—C Bonds

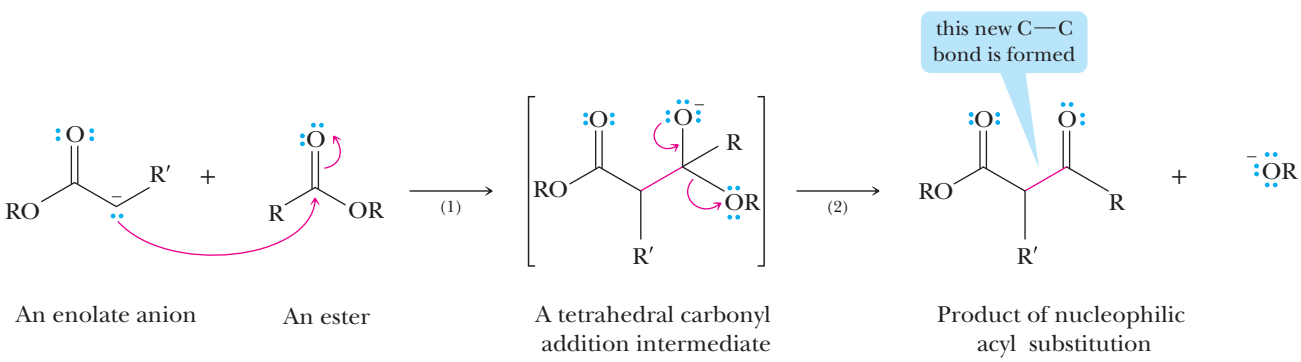
Enolate anions are important building blocks in organic synthesis, and we will study their use as nucleophiles to form new carbon–carbon bonds. In overview, they participate in three types of nucleophilic reactions.

Enolate anions function as nucleophiles in carbonyl addition reactions:



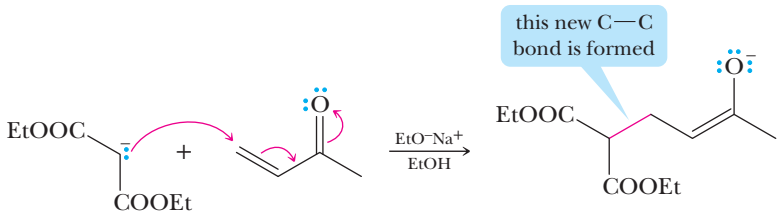
This type of enolate anion reaction is particularly useful among reactions of aldehydes and ketones in the aldol reaction (Section 15.2).

Enolate anions function as nucleophiles in nucleophilic acyl substitution reactions:



This type of enolate anion reaction occurs among esters in the Claisen (Section 15.3A) and Dieckmann condensations (Section 15.3B).

Enolate anions undergo nucleophilic addition to a carbon–carbon double bond if the double bond is conjugated with the carbonyl group of an aldehyde, a ketone, or an ester:



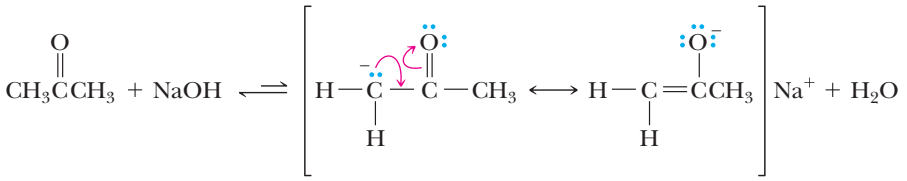
Enolate anion of diethyl propanedioate (Diethyl malonate) — 3-Buten-2-one (Methyl vinyl ketone)

This type of enolate anion reaction is called the Michael reaction (Section 15.5).

15.2 What Is the Aldol Reaction?

A. Formation of Enolate Anions of Aldehydes and Ketones

Treatment of an aldehyde or a ketone containing an acidic α-hydrogen with a strong base, such as sodium hydroxide or sodium ethoxide, gives an enolate anion as a hybrid of two major contributing structures:

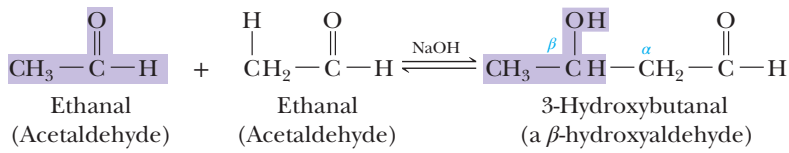


pK_a 20 (weaker acid) — An enolate anion — pK_a 15.7 (stronger acid)

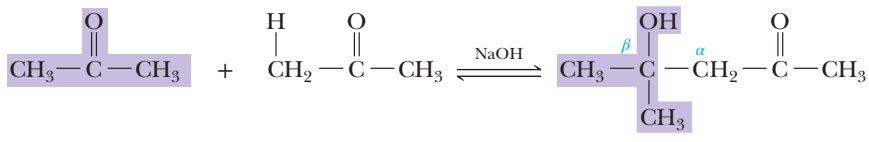
Given the relative acidities of the two acids in this equilibrium, the position of equilibrium lies considerably to the left. However, the existence of just a small amount of enolate anion is enough to allow the aldol reaction to proceed.

B. The Aldol Reaction

Addition of the enolate anion derived from an aldehyde or a ketone to the carbonyl group of another aldehyde or ketone is illustrated by these examples:



Ethanal (Acetaldehyde) — Ethanal (Acetaldehyde) — 3-Hydroxybutanal (a β-hydroxyaldehyde)



Propanone (Acetone) — Propanone (Acetone) — 4-Hydroxy-4-methyl-2-pentanone (a β-hydroxyketone)

The common name of the product derived from the reaction of acetaldehyde in base is **aldol**, so named because it is both an **ald**ehyde and an alcoh**ol**. *Aldol* is also the generic name given to any product formed in this type of reaction. The functional group of the product of an **aldol reaction** is a β-hydroxyaldehyde or a β-hydroxyketone.

Aldol reaction A carbonyl condensation reaction between two aldehydes or ketones to give a β-hydroxyaldehyde or a β-hydroxyketone.

The key step in a base-catalyzed aldol reaction is nucleophilic addition of the enolate anion from one carbonyl-containing molecule to the carbonyl group of another carbonyl-containing molecule to form a tetrahedral carbonyl addition intermediate. This mechanism is illustrated by the aldol reaction between two molecules of acetaldehyde. Notice that OH^- is a true catalyst: An OH^- is used in Step 1, but another OH^- is generated in Step 3. Notice also the parallel between Step 2 of the aldol reaction and the reaction of Grignard reagents with aldehydes and ketones (Section 12.5) and the first step of their reaction with esters (Section 14.7). Each type of reaction involves the addition of a carbon nucleophile to the carbonyl carbon of another molecule.

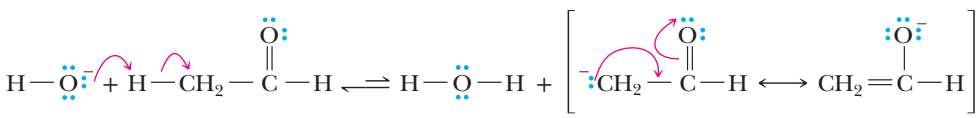
β-Hydroxyaldehydes and β-hydroxyketones are very easily dehydrated, and often the conditions necessary to bring about an aldol reaction are sufficient to cause dehydration (Section 8.2E). Dehydration can also be brought about by warming the aldol product in dilute acid. The major product from the dehydration of an aldol product is one in which the carbon–carbon double bond is conjugated with the carbonyl group; that is, the product

Mechanism

Base-Catalyzed Aldol Reaction

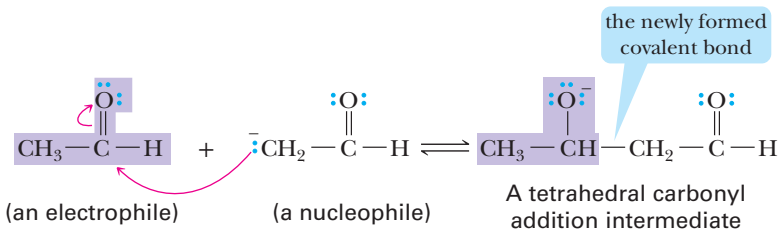
STEP 1: *Take a proton away.*

The removal of an α-hydrogen by base gives a resonance-stabilized enolate anion:



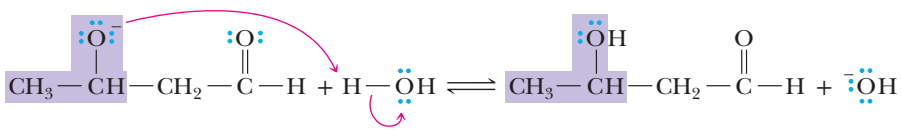
STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*

Because the equilibrium favors the left in Step 1, there is plenty of unreacted aldehyde (or ketone) remaining in the reaction mixture. Nucleophilic addition of the enolate anion to the carbonyl carbon of an unreacted molecule of aldehyde (or ketone) gives a tetrahedral carbonyl addition intermediate:



STEP 3: *Add a proton.*

Reaction of the tetrahedral carbonyl addition intermediate with a proton donor gives the aldol product and generates another hydroxide ion:



EXAMPLE 15.2

Draw the product of the base-catalyzed aldol reaction of each compound:
(a) Butanal **(b)** Cyclohexanone

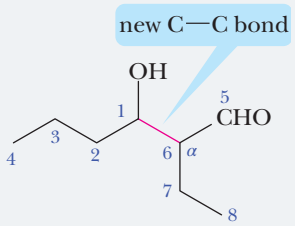
STRATEGY

Draw two molecules of each ketone or aldehyde. Convert one of the molecules to an enolate anion and show it adding to the carbonyl carbon of the other. Be sure to show the regeneration of base accompanied by the formation of the β-hydroxycarbonyl. It often helps to number the atoms in the enolate anion and the ketone or aldehyde.

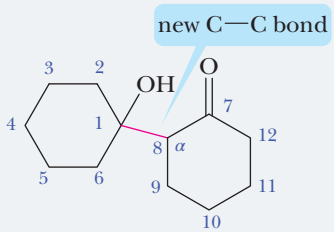
SOLUTION

The aldol product is formed by the nucleophilic addition of the α-carbon of one compound to the carbonyl carbon of another:

(a)



(b)

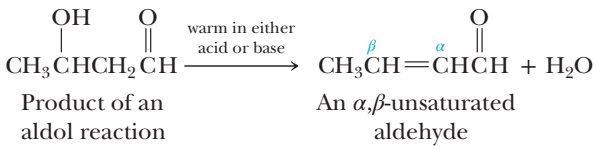


See problems 15.17, 15.20, 15.21

PROBLEM 15.2

Draw the product of the base-catalyzed aldol reaction of each compound:
(a) Acetophenone **(b)** Cyclopentanone **(c)** 3-pentanone

is an **α,β-unsaturated aldehyde or ketone** (so named because the site of unsaturation, the double bond, is between the α and β carbons).



Base-catalyzed aldol reactions are readily reversible, and generally little aldol product is present at equilibrium. Equilibrium constants for dehydration, however, are usually large, so that, if reaction conditions are sufficiently vigorous to bring about dehydration, good yields of product can be obtained.

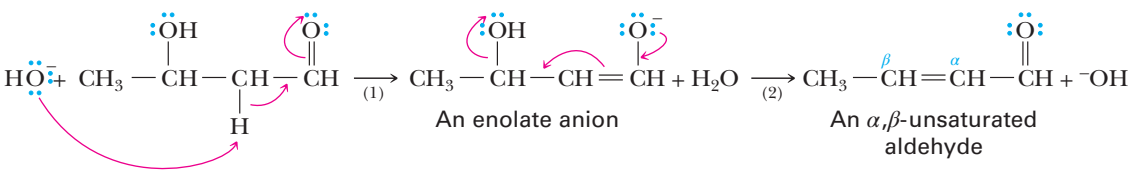
Mechanism

Base-Catalyzed Dehydration of an Aldol Product

We can write the following two-step mechanism for the base-catalyzed dehydration of an aldol product:

STEP 1: *Take a proton away.*
An acid–base reaction removes an α-hydrogen to give an enolate anion.

STEP 2: *Break a bond to form a stable molecule.*
The enolate anion ejects hydroxide ion, regenerating the base and giving the α,β-unsaturated carbonyl compound.



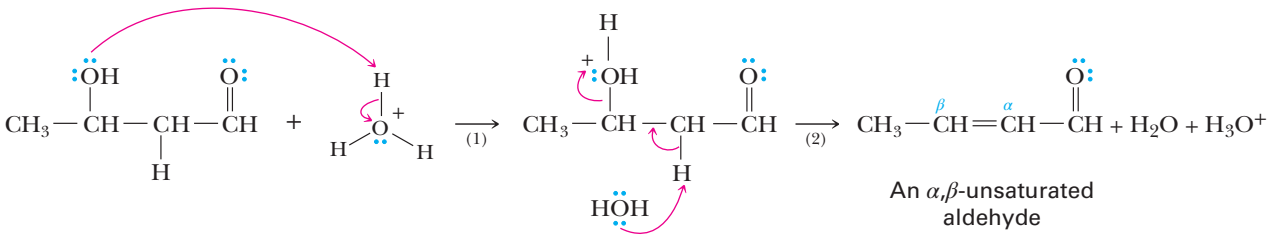
Mechanism

Acid-Catalyzed Dehydration of an Aldol Product

The acid-catalyzed dehydration of an aldol product also takes place in two steps:

STEP 1: *Add a proton.*
An acid–base reaction protonates the β-hydroxyl group.

STEP 2: *Take a proton away and break a bond to form a stable molecule.*
Water acts as a base to abstract an α-hydrogen and eject H_2O as a leaving group, giving the α,β-unsaturated carbonyl compound and regenerating the acid.



EXAMPLE 15.3

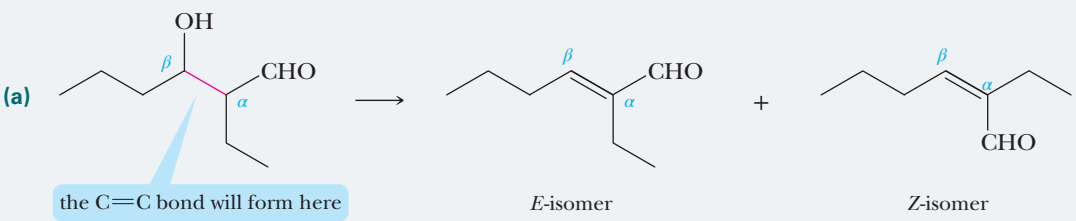
Draw the product of the base-catalyzed dehydration of each aldol product from Example 15.2.

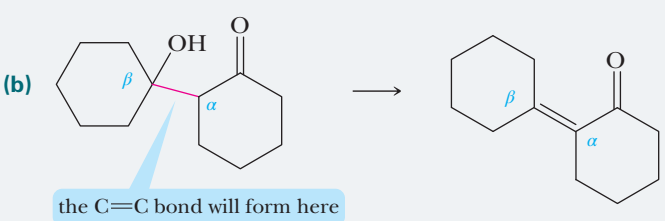
STRATEGY

The product of dehydration of an aldol product is always an α,β-unsaturated carbonyl compound. The C—C double bond always forms between the α-carbon and the carbon that was once bonded to the —OH group.

SOLUTION

Loss of H_2O from aldol product (a) gives two isomeric α,β-unsaturated aldehydes, while loss of H_2O from aldol product (b) gives an α,β-unsaturated ketone:





See problems 15.17, 15.18, 15.20–15.24

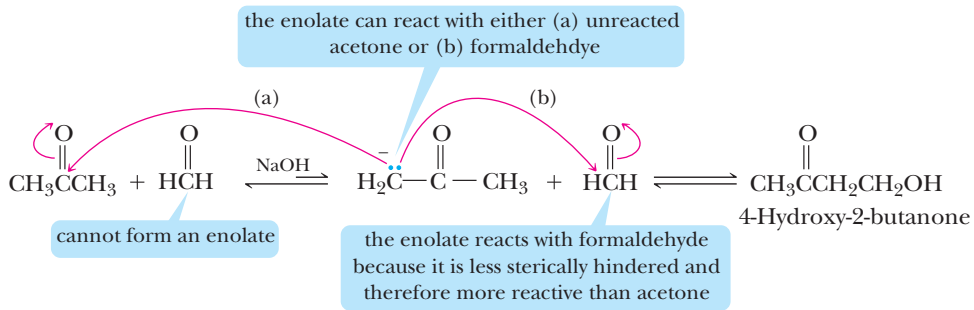
PROBLEM 15.3

Draw the product of the base-catalyzed dehydration of each aldol product from Problem 15.2.

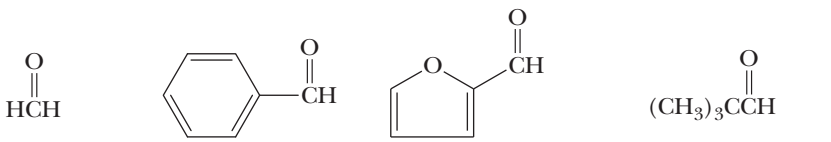
C. Crossed Aldol Reactions

Crossed aldol reaction An aldol reaction between two different aldehydes, two different ketones, or an aldehyde and a ketone.

The reactants in the key step of an aldol reaction are an enolate anion and an enolate anion acceptor. In self-reactions, both roles are played by one kind of molecule. **Crossed aldol reactions** are also possible, such as the crossed aldol reaction between acetone and formaldehyde. Because it has no α-hydrogen, formaldehyde cannot form an enolate anion. It is, however, a particularly good enolate anion acceptor because its carbonyl group is unhindered. Acetone forms an enolate anion, but its carbonyl group, which is bonded to two alkyl groups, is less reactive than that of formaldehyde. Consequently, the crossed aldol reaction between acetone and formaldehyde gives 4-hydroxy-2-butanone:



As this example illustrates, for a crossed aldol reaction to be successful, one of the two reactants should have no α-hydrogen, so that its enolate anion does not form. It also helps if the compound with no α-hydrogen has the more reactive carbonyl—for example, an aldehyde. Following are examples of aldehydes that have no α-hydrogens and that can be used in crossed aldol reactions:



Formaldehyde Benzaldehyde Furfural 2,2-Dimethylpropanal

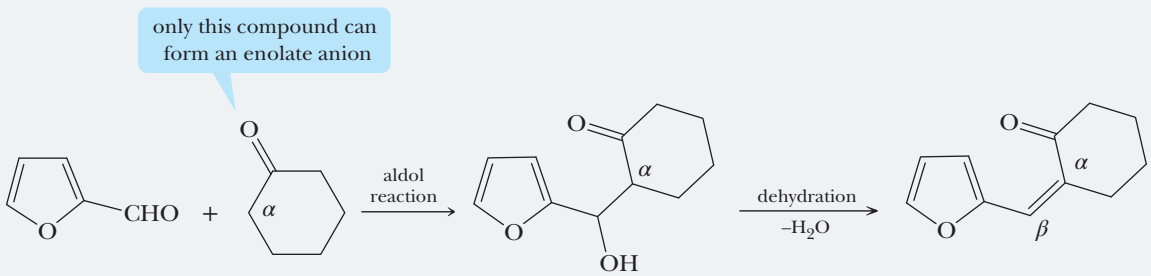
EXAMPLE 15.4

Draw the product of the crossed aldol reaction between furfural and cyclohexanone and the product formed by its base-catalyzed dehydration.

STRATEGY

Determine which carbonyl compound possesses an abstractable α-hydrogen and draw its enolate anion. Decide which carbonyl compound would be more reactive toward the enolate anion (aldehydes are more reactive than ketones) and show the enolate anion adding to its carbonyl carbon to form a β-hydroxycarbonyl. It often helps to number the atoms in the enolate anion and the ketone or aldehyde. The product of dehydration of an aldol product is always an α,β-unsaturated carbonyl compound. The C—C double bond always forms between the α-carbon and the carbon that was once bonded to the —OH group.

SOLUTION



Furfural Cyclohexanone Aldol product

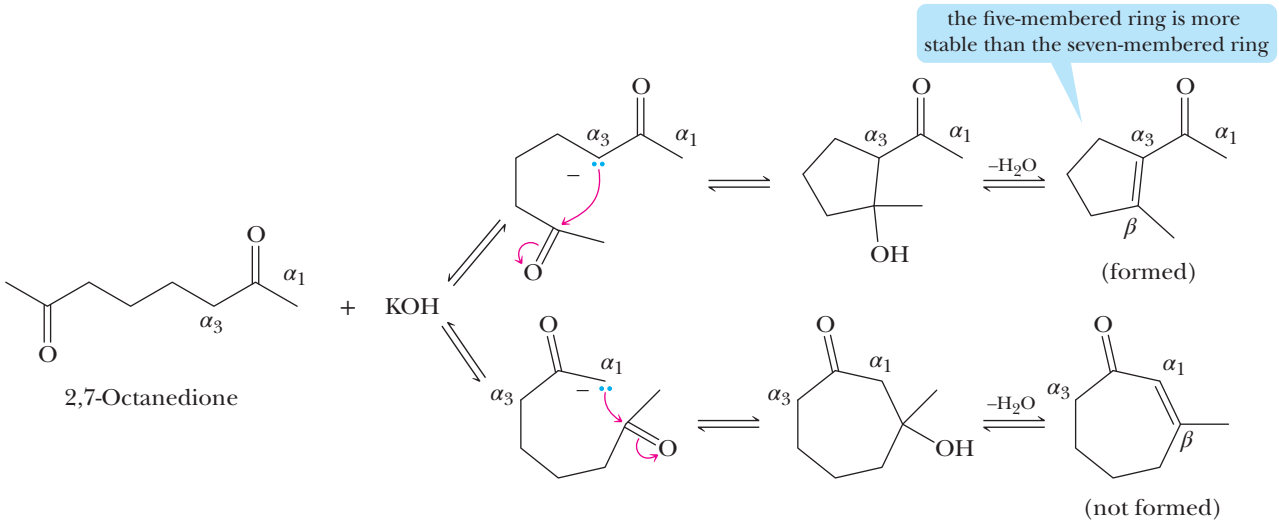
See problems 15.18, 15.19

PROBLEM 15.4

Draw the product of the crossed aldol reaction between benzaldehyde and 3-pentanone and the product formed by its base-catalyzed dehydration.

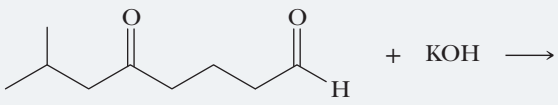
D. Intramolecular Aldol Reactions

When both the enolate anion and the carbonyl group to which it adds are in the same molecule, aldol reaction results in formation of a ring. This type of **intramolecular aldol reaction** is particularly useful for the formation of five- and six-membered rings. Because they are the most stable rings, and because the equilibrium conditions under which these reactions are performed are driven by stability, five- and six-membered rings form much more readily than four- or seven- and larger-membered rings. Intramolecular aldol reaction of 2,7-octanedione via enolate anion α_3, for example, gives a five-membered ring, whereas intramolecular aldol reaction of this same compound via enolate anion α_1 would give a seven-membered ring. In the case of 2,7-octanedione, the five-membered ring forms in preference to the seven-membered ring:



EXAMPLE 15.5

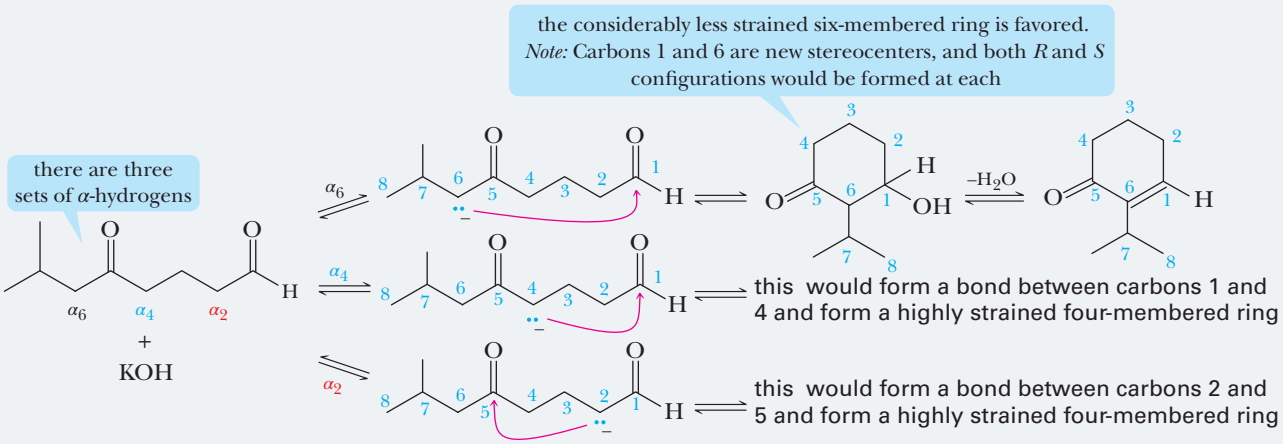
Draw the dehydration product of the following intramolecular aldol reaction.



STRATEGY

Identify all the alpha hydrogens in the molecule, and for each one, form an enolate anion. Then decide which enolate anion would form the more stable ring upon reaction with the other carbonyl in the molecule. It often helps to number the atoms in the ketone or aldehyde. The product of dehydration of any aldol product is always an α,β-unsaturated carbonyl compound. The C—C double bond always forms between the α-carbon and the carbon that was once bonded to the —OH group.

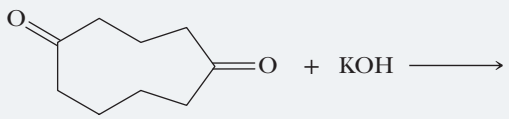
SOLUTION



See problems 15.22–15.24

PROBLEM 15.5

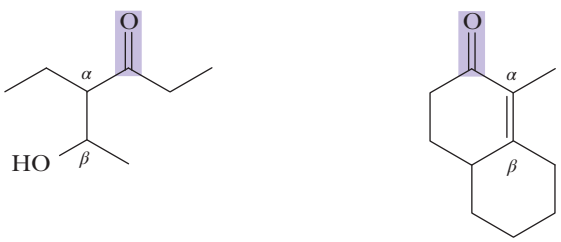
Draw the dehydration product of the following intermolecular aldol reaction.



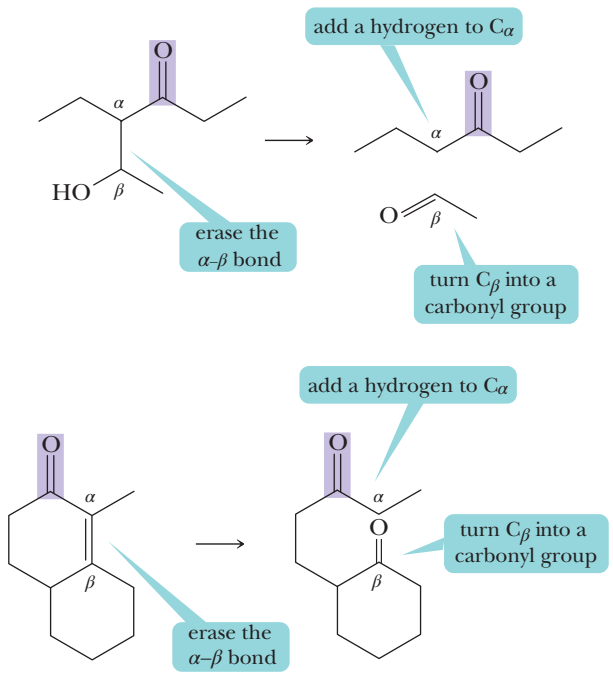
HOW TO 15.1 Determine the Starting Compounds Used in an Aldol Reaction

It will sometimes be necessary to work retrosynthetically (How To 14.2) from the product of an aldol reaction. Following are the steps for determining the starting compounds used in an aldol reaction.

(a) Locate the carbonyl and identify the α- and β-carbons. An aldol product will contain a carbonyl of a ketone or an aldehyde and either an OH group or a C—C double bond. Once the carbonyl is found, label the carbons using the Greek alphabet in the direction of the OH group or C—C double bond:



(b) Erase the bond between the α- and β-carbons and convert the carbon labeled β to a carbonyl group (the oxygen of an —OH group bonded to the β-carbon becomes the oxygen atom of the carbonyl). Note that a hydrogen is added to the carbon labeled α, although it is usually unnecessary to show this in a line-angle formula:

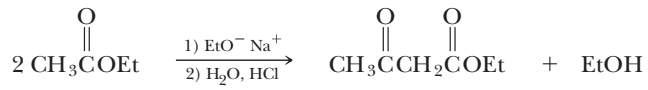


15.3 What Are the Claisen and Dieckmann Condensations?

A. Claisen Condensation

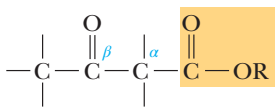
In this section, we examine the formation of an enolate anion from one ester, followed by the nucleophilic acyl substitution of the enolate anion at the carbonyl carbon of another ester. One of the first of these reactions discovered was the **Claisen condensation**, named after its discoverer, German chemist Ludwig Claisen (1851–1930). We illustrate a Claisen condensation by the reaction between two molecules of ethyl acetate in the presence of sodium ethoxide, followed by acidification, to give ethyl acetoacetate (note that, in this and many of the equations that follow, we abbreviate the ethyl group as Et):

Claisen condensation
A carbonyl condensation reaction between two esters to give a β-ketoester.



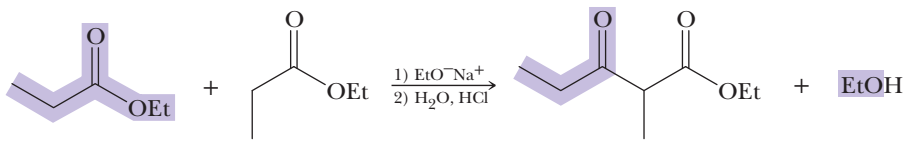
Ethyl ethanoate (Ethyl acetate) — Ethyl 3-oxobutanoate (Ethyl acetoacetate) — Ethanol

The functional group of the product of a Claisen condensation is a ***β*-ketoester**:



A β-ketoester

The Claisen condensation of two molecules of ethyl propanoate gives the following β-ketoester:



Ethyl propanoate — Ethyl propanoate — Ethyl 2-methyl-3-oxopentanoate (racemic)

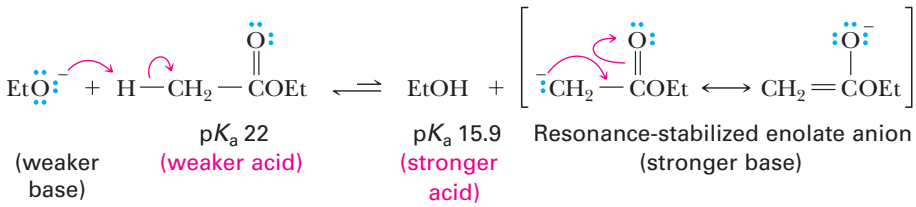
Claisen condensations, like the aldol reaction, require a base. Aqueous bases, such as NaOH, however, cannot be used in Claisen condensations because aqueous base would bring about hydrolysis of the ester (saponification, Section 14.3C) instead. Rather, the bases most commonly used in Claisen condensations are nonaqueous bases, such as sodium ethoxide in ethanol and sodium methoxide in methanol. Furthermore, to prevent transesterification (Section 14.4C), the alkyl group (—R) of the base should match the R group in the alkoxyl portion (—OR) of the ester.

Mechanism

Claisen Condensation

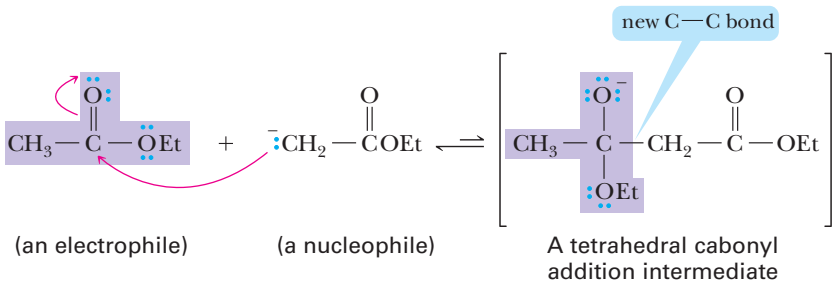
As you study this mechanism, note how closely its first two steps resemble the first steps of the aldol reaction (Section 15.1). In each reaction, base removes a proton from an α-carbon in Step 1 to form a resonance-stabilized enolate anion. In Step 2, the enolate anion attacks the carbonyl carbon of another ester molecule to form a tetrahedral carbonyl addition intermediate.

STEP 1: *Take a proton away.*
Base removes an α-hydrogen from the ester to give a resonance-stabilized enolate anion:

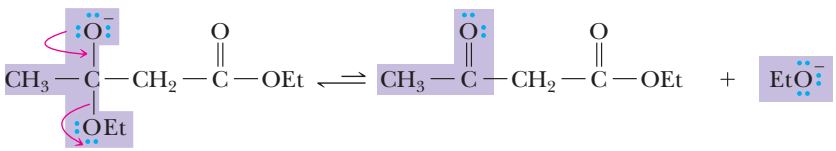


Because the α-hydrogen of the ester is the weaker acid and ethoxide is the weaker base, the position of this equilibrium lies very much toward the left.

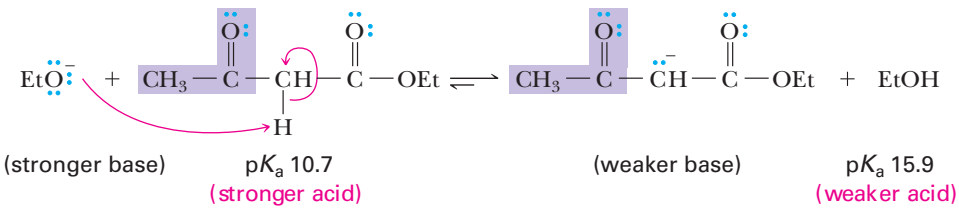
STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*
Attack of the enolate anion on the carbonyl carbon of another ester molecule gives a tetrahedral carbonyl addition intermediate:



STEP 3: *Collapse of the tetrahedral carbonyl addition intermediate to eject a leaving group and regenerate the carbonyl group.*
Unlike the tetrahedral carbonyl addition intermediate in the aldol reaction, this intermediate has a leaving group (the ethoxide ion). Collapse of the tetrahedral carbonyl addition intermediate by ejection of the ethoxide ion gives a β-ketoester:

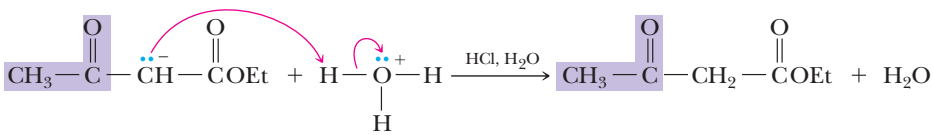


STEP 4: *Take a proton away.*
Formation of the enolate anion of the β-ketoester drives the Claisen condensation to the right. The β-ketoester (a stronger acid) reacts with ethoxide ion (a stronger base) to give ethanol (a weaker acid) and the anion of the β-ketoester (a weaker base):



The position of equilibrium for this step lies very far toward the right.

STEP 5: *Add a proton.*
Acidification of the enolate anion gives the β-ketoester:



EXAMPLE 15.6

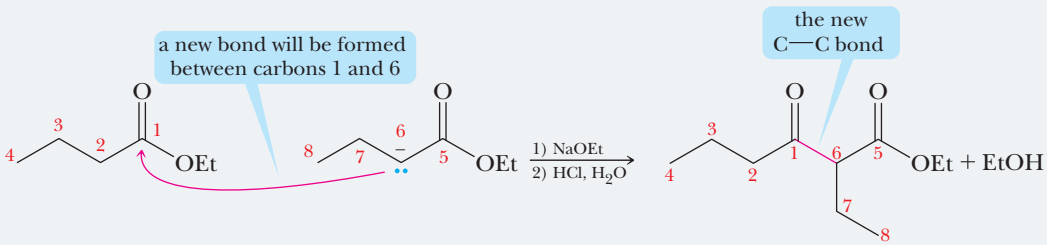
Show the product of the Claisen condensation of ethyl butanoate in the presence of sodium ethoxide followed by acidification with aqueous HCl.

STRATEGY

Draw two molecules of ethyl butanoate. Convert one of the molecules to an enolate anion and show it adding to the carbonyl carbon of the other. Because Claisen condensations occur with nucleophilic acyl substitution, the —OR group of the carbonyl being attacked is eliminated from the final product. It often helps to number the atoms in the enolate anion and the ester being attacked.

SOLUTION

The new bond formed in a Claisen condensation is between the carbonyl group of one ester and the α-carbon of another:



Ethyl butanoate | Enolate of ethyl butanoate | Ethyl 2-ethyl-3-oxohexanoate (racemic)

See problem 15.27

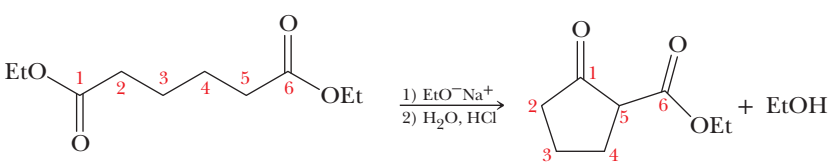
PROBLEM 15.6

Show the product of the Claisen condensation of ethyl 3-methylbutanoate in the presence of sodium ethoxide.

B. Dieckmann Condensation

An intramolecular Claisen condensation of a dicarboxylic ester to give a five- or six-membered ring is known as a **Dieckmann condensation**. In the presence of one equivalent of sodium ethoxide, diethyl hexanedioate (diethyl adipate), for example, undergoes an intramolecular condensation to form a five-membered ring:

Dieckmann condensation
An intramolecular Claisen condensation of an ester of a dicarboxylic acid to give a five- or six-membered ring.

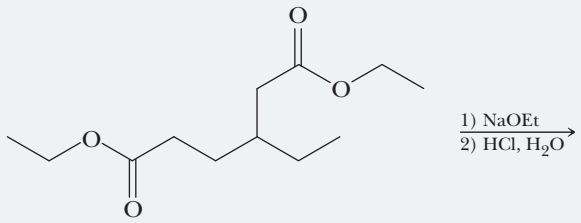


Diethyl hexanedioate (Diethyl adipate) | Ethyl 2-oxocyclopentanecarboxylate

The mechanism of a Dieckmann condensation is identical to the mechanism we described for the Claisen condensation. An anion formed at the α-carbon of one ester in Step 1 adds to the carbonyl of the other ester group in Step 2 to form a tetrahedral carbonyl addition intermediate. This intermediate ejects ethoxide ion in Step 3 to regenerate the carbonyl group. Cyclization is followed by formation of the conjugate base of the β-ketoester in Step 4, just as in the Claisen condensation. The β-ketoester is isolated after acidification with aqueous acid.

EXAMPLE 15.7

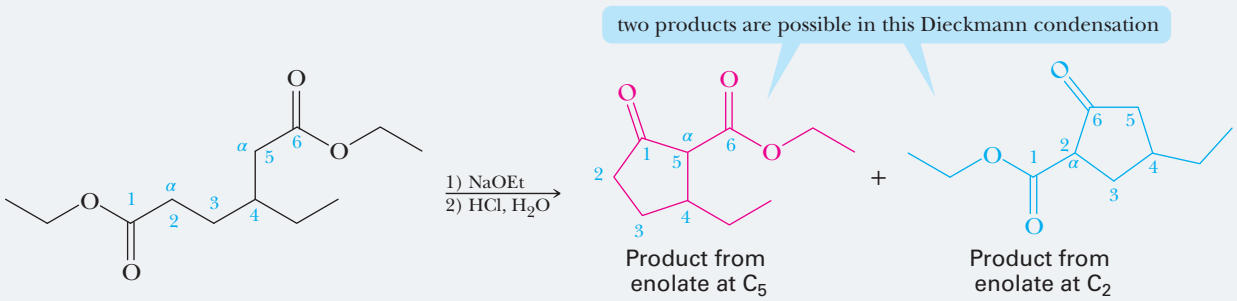
Complete the equation for the following Dieckmann condensation (disregard the stereochemistry for this example):



STRATEGY

Identify the α-carbon for each ester group. Convert one of the α-carbons to an enolate anion and show it adding to the other carbonyl carbon. Because Dieckmann condensations occur with nucleophilic acyl substitution, the —OR group of the carbonyl being attacked is eliminated from the final product. It often helps to number the atoms in the enolate anion and the ester being attacked.

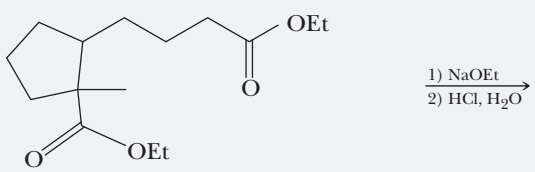
SOLUTION



See problem 15.33

PROBLEM 15.7

Complete the equation for the following Dieckmann condensation (disregard the stereochemistry for this example):



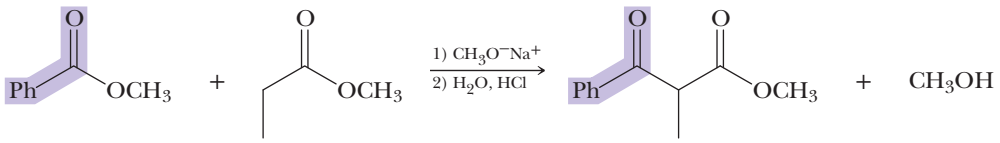
C. Crossed Claisen Condensations

Crossed Claisen condensation A Claisen condensation between two different esters.

In a **crossed Claisen condensation** (a Claisen condensation between two different esters, each with its own α-hydrogens), a mixture of four β-ketoesters is possible; therefore, crossed Claisen condensations of this type are generally not synthetically useful. Such condensations are useful, however, if appreciable differences in reactivity exist between the two esters, as, for example, when one of the esters has no α-hydrogens and can function only as an enolate anion acceptor. These esters have no α-hydrogens:

Ethyl formate | Diethyl carbonate | Diethyl ethanedioate (Diethyl oxalate) | Ethyl benzoate

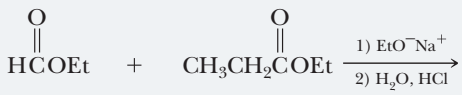
Crossed Claisen condensations of this type are usually carried out by using the ester with no α-hydrogens in excess. In the following illustration, methyl benzoate is used in excess:



Methyl benzoate | Methyl propanoate | Methyl 2-methyl-3-oxo-3-phenylpropanoate

EXAMPLE 15.8

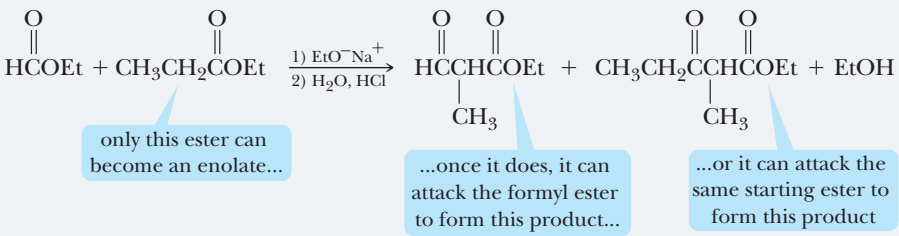
Complete the equation for this crossed Claisen condensation:



STRATEGY

Identify the α-carbon(s) for each ester. Convert one of the α-carbons to an enolate anion and show it adding to the other carbonyl carbon. Repeat this for all α-carbons and ester molecules. Remember that the enolate anion can attack the other ester or an unreacted molecule of itself if equal amounts of ester are used. Because Claisen condensations occur with nucleophilic acyl substitution, the —OR group of the carbonyl being attacked is eliminated from the final product. It often helps to number the atoms in the enolate anion and the ester being attacked.

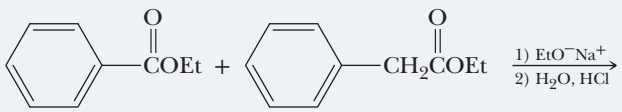
SOLUTION



See problems 15.29–15.31

PROBLEM 15.8

Complete the equation for this crossed Claisen condensation:

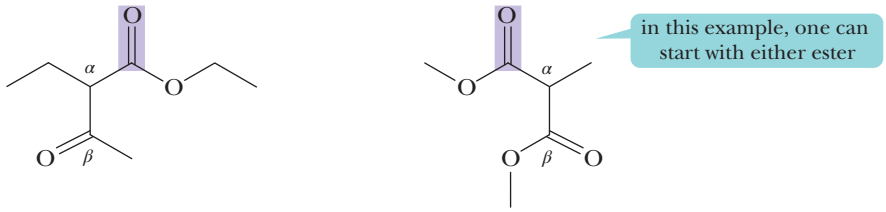


HOW TO 15.2

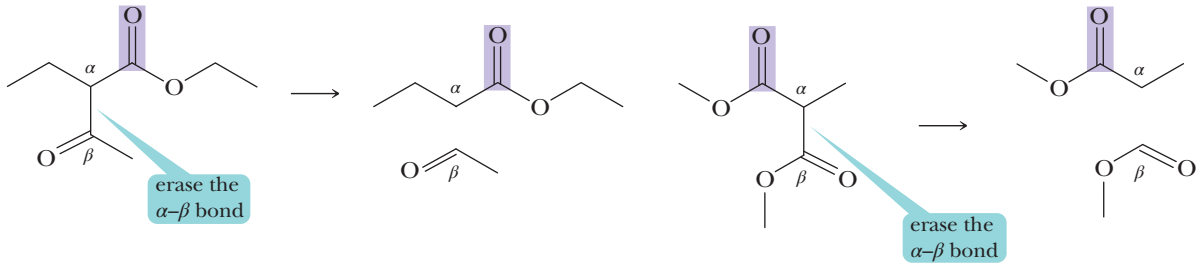
Determine the Starting Compounds Used in a Claisen Condensation

It will sometimes be necessary to work retrosynthetically (HowTo 14.2) from the product of a Claisen condensation. Following are the steps for determining the starting compounds used in a Claisen condensation.

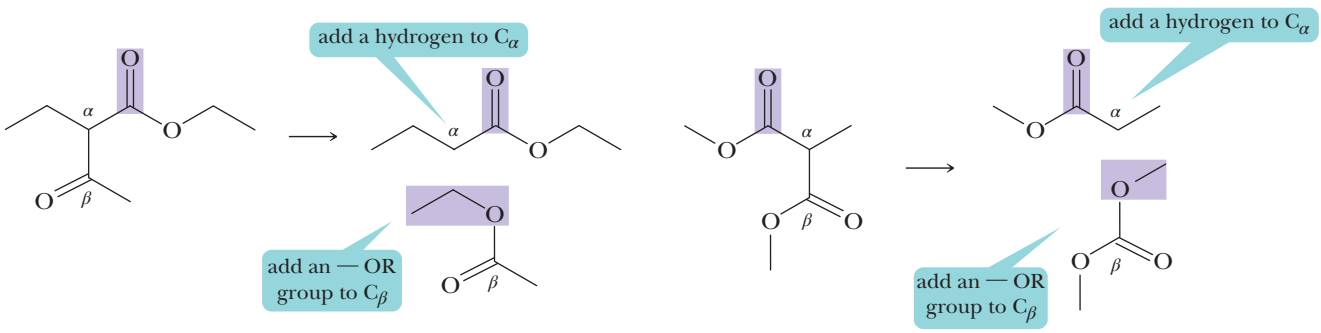
(a) Locate the carbonyl of an ester and identify the α- and β-carbons. A Claisen condensation product will contain a carbonyl of an ester and another carbonyl of either an aldehyde, a ketone, or another ester. Once the carbonyl of the ester is found, label the carbons using the Greek alphabet in the direction of the other carbonyl group:



(b) Erase the bond between the α- and β-carbons:



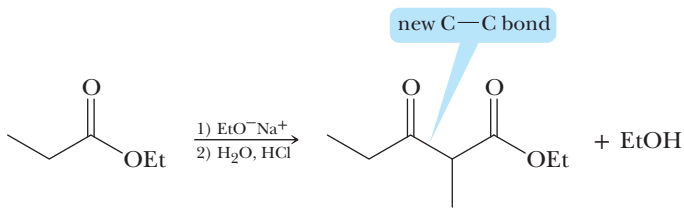
(c) Add a hydrogen to the carbon labeled α and add an —OR group to the carbon labeled β. The type of alkyl group in —OR should match the alkyl group of the other ester:



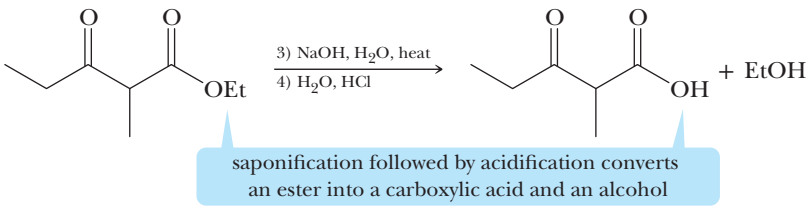
D. Hydrolysis and Decarboxylation of β-Ketoesters

Recall from Section 14.3C that the hydrolysis of an ester in aqueous sodium hydroxide (saponification), followed by acidification of the reaction mixture with HCl or other mineral acid, converts an ester to a carboxylic acid and an alcohol. Recall also from Section 13.8 that β-ketoacids and β-dicarboxylic acids readily undergo decarboxylation (lose CO_2) when heated. The following equations illustrate the results of a Claisen condensation, followed by saponification, acidification, and decarboxylation:

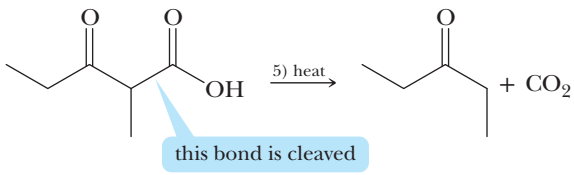
Claisen condensation:



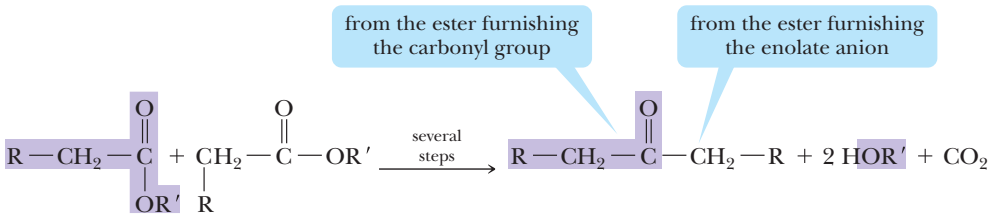
Saponification followed by acidification:



Decarboxylation:



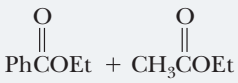
The result of these five steps is a reaction between two molecules of ester, one furnishing a carbonyl group and the other furnishing an enolate anion, to give a ketone and carbon dioxide:

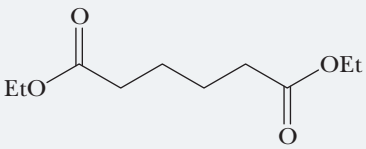


In the general reaction, both ester molecules are the same, and the product is a symmetrical ketone.

EXAMPLE 15.9

Each set of compounds undergoes (1, 2) Claisen condensation, (3) saponification followed by (4) acidification, and (5) thermal decarboxylation:

(a) 

(b) 

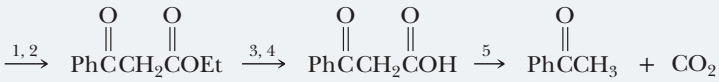
Draw a structural formula of the product after completion of this reaction sequence.

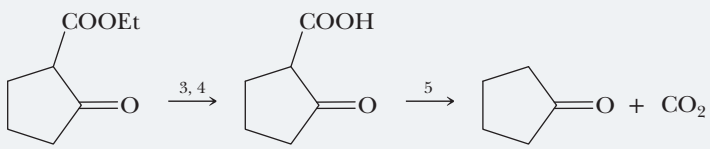
STRATEGY

Proceed with a variation of the Claisen condensation (Examples 15.6–15.8) and arrive at the final decarboxylated product by removing the carbonyl ester group and replacing it with a hydrogen.

SOLUTION

Steps 1 and 2 bring about a crossed Claisen condensation in (a) and a Dieckmann condensation in (b) to form a β-ketoester. Steps 3 and 4 bring about hydrolysis of the β-ketoester to give a β-ketoacid, and Step 5 brings about decarboxylation to give a ketone:

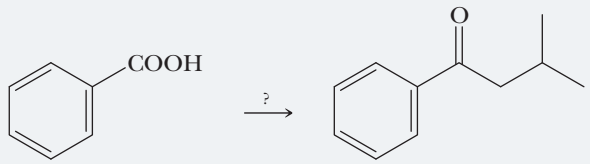
(a) 

(b) 

See problems 15.28, 15.32, 15.34

PROBLEM 15.9

Show how to convert benzoic acid to 3-methyl-1-phenyl-1-butanone by using a Claisen condensation at some stage in the synthesis:

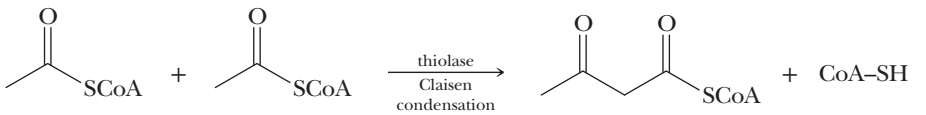


Benzoic acid 3-Methyl-1-phenyl-1-butanone

15.4 How Are Aldol Reactions and Claisen Condensations Involved in Biological Processes?

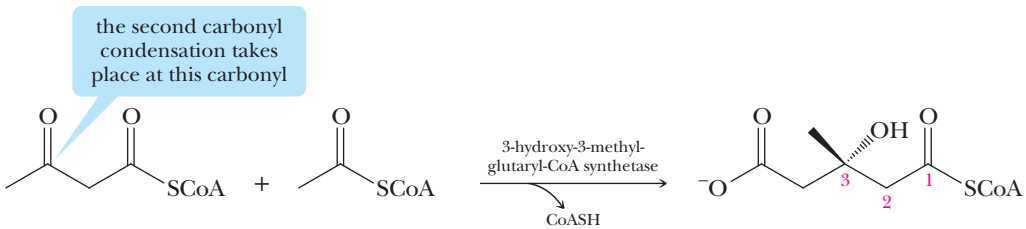
Carbonyl condensations are among the most widely used reactions in the biological world for the assembly of new carbon–carbon bonds in such important biomolecules as fatty acids, cholesterol, and steroid hormones. One source of carbon atoms for the synthesis of these biomolecules is **acetyl-CoA**, a thioester of acetic acid and the thiol group of coenzyme A. The function of the coenzyme A group of acetyl-CoA is to anchor the acetyl group on the surface of the enzyme systems that catalyze the reactions we examine in this section. In the discussions that follow, we will not be concerned with the mechanism by which each enzyme-catalyzed reaction occurs. Rather, our concern is with recognizing the type of reaction that takes place in each step.

In the Claisen condensation catalyzed by the enzyme thiolase, acetyl-CoA is converted to its enolate anion, which then attacks the carbonyl group of a second molecule of acetyl-CoA to form a tetrahedral carbonyl addition intermediate. Collapse of this intermediate by the loss of CoA-SH gives acetoacetyl-CoA. The mechanism for this condensation reaction is exactly the same as that of the Claisen condensation (Section 15.3A):



Acetyl-CoA Acetyl-CoA Acetoacetyl-CoA Coenzyme A

An enzyme-catalyzed aldol reaction with a third molecule of acetyl-CoA on the ketone carbonyl of acetoacetyl-CoA gives (*S*)-3-hydroxy-3-methylglutaryl-CoA:



(*S*)-3-Hydroxy-3-methylglutaryl-CoA

Note three features of this reaction. First, the creation of the new stereocenter is stereoselective: Only the S enantiomer is formed. Although the acetyl group of each reactant is achiral, their condensation takes place in a chiral environment created by the enzyme 3-hydroxy-3-methylglutaryl-CoA synthetase. Second, hydrolysis of the thioester group of

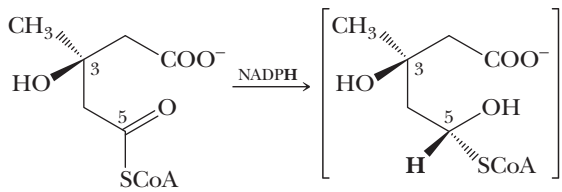
Chemical Connections 15A

DRUGS THAT LOWER PLASMA LEVELS OF CHOLESTEROL

Coronary artery disease is the leading cause of death in the United States and other Western countries, where about one half of all deaths can be attributed to atherosclerosis. Atherosclerosis results from the buildup of fatty deposits called plaque on the inner walls of arteries. A major component of plaque is cholesterol derived from low-density-lipoproteins (LDL), which circulate in blood plasma. Because more than one half of total body cholesterol in humans is synthesized in the liver from acetyl-CoA, intensive efforts have been directed toward finding ways to inhibit this synthesis. The rate-determining step in cholesterol biosynthesis is reduction of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) to mevalonic acid. This reduction is catalyzed by the enzyme HMG-CoA reductase and requires two moles of NADPH per mole of HMG-CoA.

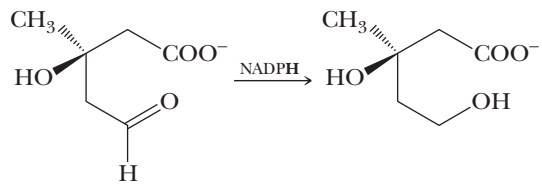
Beginning in the early 1970s, researchers at the Sankyo Company in Tokyo screened more than 8,000 strains of microorganisms and in 1976 announced the isolation of mevastatin, a potent inhibitor of HMG-CoA reductase, from culture broths of the fungus *Penicillium citrinum*. The same compound was isolated by researchers at Beecham Pharmaceuticals in England from cultures of *Penicillium brevicompactum*. Soon thereafter, a second, more active compound called lovastatin was isolated at the Sankyo Company from the fungus *Monascus ruber*, and at Merck Sharpe & Dohme from *Aspergillus terreus*. Both mold metabolites are extremely effective in lowering plasma concentrations of LDL. The active form of each is the 5-hydroxycarboxylate anion formed by hydrolysis of the δ-lactone.

These drugs and several synthetic modifications now available inhibit HMG-CoA reductase by forming an enzyme-inhibitor complex that prevents further catalytic action of the enzyme. It is reasoned that the 3,5-dihydroxycarboxylate anion part of the active form of each drug binds tightly to the enzyme because it mimics the hemithioacetal intermediate formed by the first reduction of HMG-CoA.



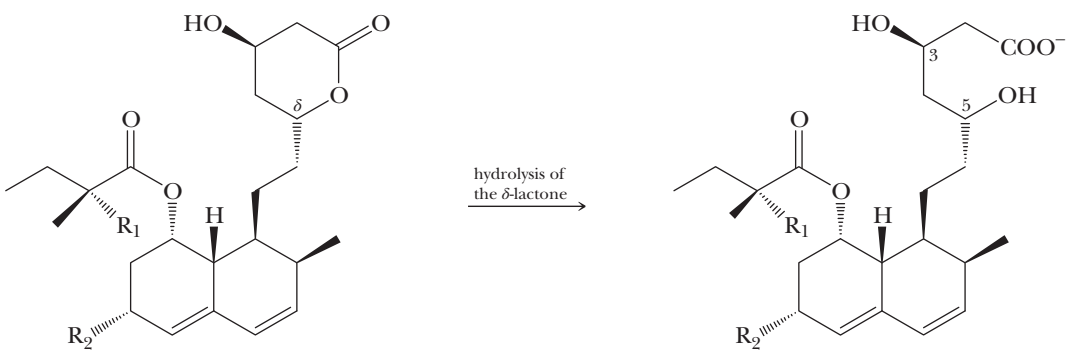
3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA)

A hemithioacetal intermediate formed by the first NADPH reduction



Mevalonate

Systematic studies have shown the importance of each part of the drug for effectiveness. It has been found, for example, that the carboxylate anion (—COO^-) is essential, as are both the 3-OH and 5-OH groups.



The active form of each drug

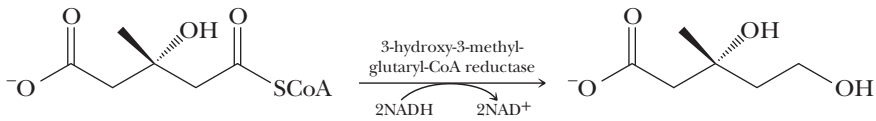
$R_1 = R_2 = H$, mevastatin
$R_1 = H$, $R_2 = CH_3$, lovastatin (Mevacor)
$R_1 = R_2 = CH_3$, simvastatin (Zocor)

Question

Which of the biomolecules in the above reaction scheme could be the product of an aldol reaction?

acetyl-CoA is coupled with the aldol reaction. Third, the carboxyl group is shown as it is ionized at pH 7.4, the approximate pH of blood plasma and many cellular fluids.

Enzyme-catalyzed reduction of the thioester group of 3-hydroxy-3-methylglutaryl-CoA to a primary alcohol gives mevalonic acid, shown here as its anion:

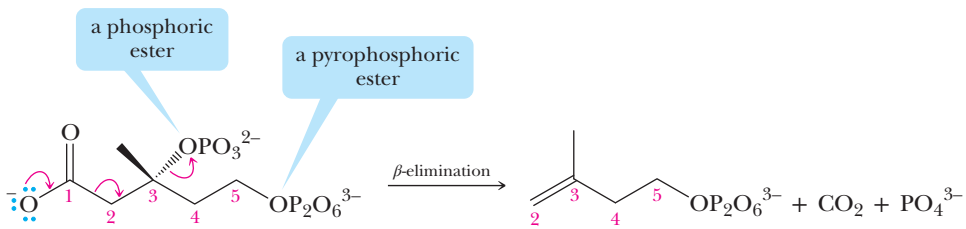


(*S*)-3-Hydroxy-3-methylglutaryl-CoA

(*R*)-Mevalonate

The reducing agent for this transformation is nicotinamide adenine dinucleotide, abbreviated NADH. This reducing agent is the biochemical equivalent of $LiAlH_4$. Each reducing agent functions by delivering a hydride ion ($H:^-$) to the carbonyl carbon of an aldehyde, a ketone, or an ester. Note that, in the reduction, a change occurs in the designation of configuration from S to R, not because of any change in configuration at the stereocenter, but rather because of a change in priority among the four groups bonded to the stereocenter.

Enzyme-catalyzed transfer of a phosphate group from adenosine triphosphate (ATP, Section 20.1) to the 3-hydroxyl group of mevalonate gives a phosphoric ester at carbon 3. Enzyme-catalyzed transfer of a pyrophosphate group (Section 14.1B) from a second molecule of ATP gives a pyrophosphoric ester at carbon 5. Enzyme-catalyzed β-elimination from this molecule results in the loss of CO_2 and PO_4^{3-}, both good leaving groups:



(*R*)-3-Phospho-5-pyrophospho-mevalonate

Isopentenyl pyrophosphate

Isopentenyl pyrophosphate is the key building block of cholesterol and all steroid hormones (Section 19.4).

15.5 What Is the Michael Reaction?

Thus far, we have used carbon nucleophiles in two ways to form new carbon–carbon bonds:

1. Addition of organomagnesium (Grignard) reagents to the carbonyl groups of aldehydes, ketones, and esters.
2. Addition of enolate anions derived from aldehydes or ketones (aldol reactions) and esters (Claisen and Dieckmann condensations) to the carbonyl groups of other aldehydes, ketones, or esters.

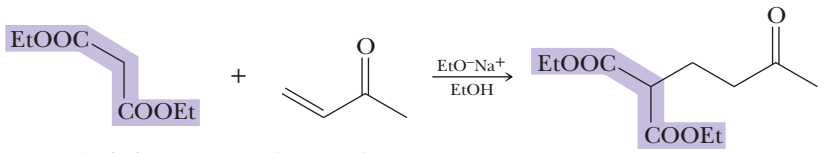
Addition of an enolate anion to a carbon–carbon double bond conjugated with a carbonyl group presents an entirely new synthetic strategy. In this section, we study a type of **conjugate addition** involving nucleophilic addition to an electrophilic double bond.

Michael reaction The conjugate addition of an enolate anion or other nucleophile to an α,β-unsaturated carbonyl compound.

A. Michael Addition of Enolate Anions

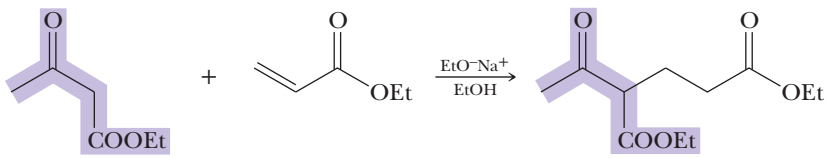
Nucleophilic addition of enolate anions to α,β-unsaturated carbonyl compounds was first reported in 1887 by the American chemist Arthur Michael. Following are two examples of **Michael reactions**. In the first example, the nucleophile is the enolate anion of

diethyl malonate. In the second example, the nucleophile is the enolate anion of ethyl acetoacetate:



Diethyl propanedioate (Diethyl malonate)

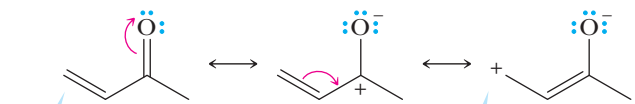
3-Buten-2-one (Methyl vinyl ketone)



Ethyl 3-oxobutanoate (Ethyl acetoacetate)

Ethyl 2-Propenoate (Ethyl acrylate)

Recall that nucleophiles don't ordinarily add to carbon–carbon double bonds. Rather, they add to electrophiles (Section 5.2). What activates a carbon–carbon double bond for nucleophilic attack in a Michael reaction is the presence of the adjacent carbonyl group. One important contributing structure of α,β-unsaturated carbonyl compounds puts a positive charge on the β-carbon of the double bond, making it electrophilic in its reactivity:



an *activated* C—C double bond due to its partial positive character as shown in one of its contributing structures

Thus, nucleophiles can add to this type of double bond, which we call "activated" for that reason.

Table 15.2 lists the most common combinations of α,β-unsaturated carbonyl compounds and nucleophiles used in Michael reactions. The most commonly used bases are metal alkoxides, pyridine, and piperidine.

TABLE 15.2 Combinations of Reagents for Effective Michael Reactions

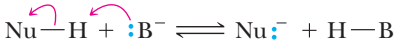
These Types of α,β-Unsaturated Compounds Are Nucleophile Acceptors in Michael Reactions		These Types of Compounds Provide Effective Nucleophiles for Michael Reactions	
$CH_2{=}CHCH$ (O)	Aldehydes	$CH_3CCHCCH_3$ (O, O, ⁻)	Enolates of β-Diketones
$CH_2{=}CHCCH_3$ (O)	Ketones	$CH_3CCHCOEt$ (O, O, ⁻)	Enolates of β-Ketoesters
$CH_2{=}CHCOEt$ (O)	Esters	$EtOCCHCOEt$ (O, O, ⁻)	Enolates of β-Diesters
		RNH_2, R_2NH	Amines

We can write the following general mechanism for a Michael reaction:

Mechanism

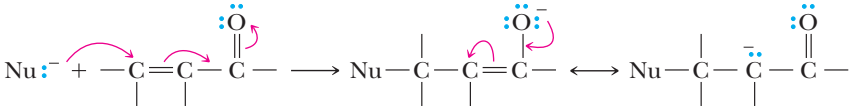
Michael Reaction—Conjugate Addition of Enolate Anions

STEP 1: *Take a proton away.*
Treatment of H—Nu with base gives the nucleophile, Nu:⁻.



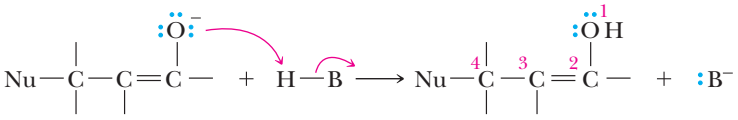
Base

STEP 2: *Reaction of an electrophile and a nucleophile to form a new covalent bond.*
Nucleophilic addition of Nu:⁻ to the β-carbon of the conjugated system gives a resonance-stabilized enolate anion:



(a nucleophile) (an electrophile) A resonance-stabilized enolate anion

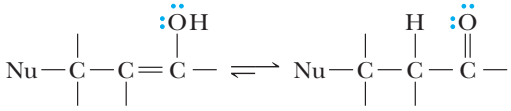
STEP 3: *Add a proton.*
Proton transfer from H—B gives the enol and regenerates the base:



An enol
(a product of 1,4-addition)

Note that the enol formed in this step corresponds to 1,4-addition to the conjugated system of the α,β-unsaturated carbonyl compound. It is because this intermediate is formed that the Michael reaction is classified as a 1,4-, or conjugate, addition. Note also that the base, B:⁻, is regenerated, in accordance with the experimental observation that a Michael reaction requires only a catalytic amount of base rather than a molar equivalent.

STEP 4: *Tautomerism.*
Tautomerism (Section 12.8A) of the less stable enol form gives the more stable keto form:



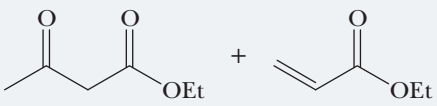
Enol form
(less stable)

Keto form
(more stable)

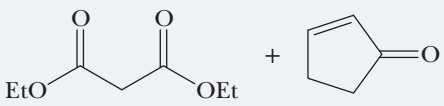
EXAMPLE 15.10

Draw a structural formula for the product formed by treating each set of reactants with sodium ethoxide in ethanol under conditions of the Michael reaction:

(a)



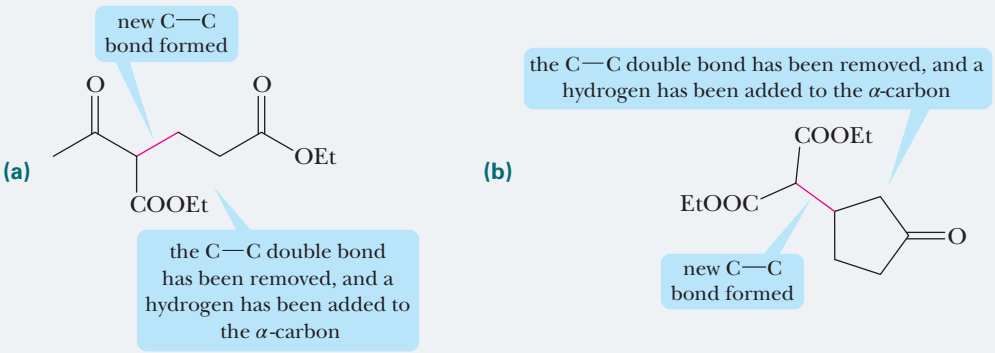
(b)



STRATEGY

The net result of a Michael reaction is the addition of a nucleophile to the β-carbon of an α,β-unsaturated carbonyl compound and the addition of a hydrogen to the α-carbon.

SOLUTION



See problems 15.35, 15.36

PROBLEM 15.10

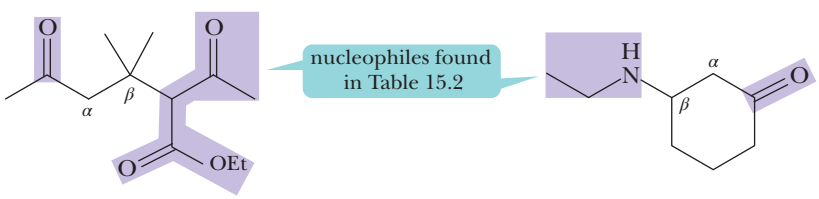
Show the product formed from each Michael reaction in the solution to Example 15.10 after (1) hydrolysis in aqueous NaOH, (2) acidification, and (3) thermal decarboxylation of each β-ketoacid or β-dicarboxylic acid. These reactions illustrate the usefulness of the Michael reaction for the synthesis of 1,5-dicarbonyl compounds.

HOW TO 15.3

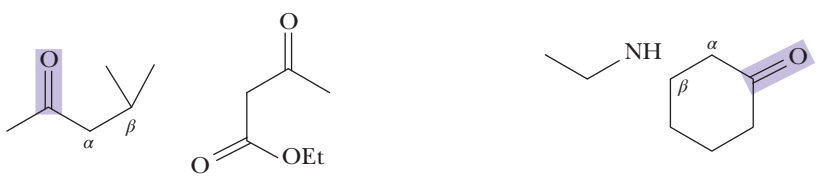
Determine the Starting Compounds Used in a Michael Reaction

It will sometimes be necessary to work retrosynthetically (How To 14.2) from the product of a Michael reaction. Following are the steps for determining the starting compounds used in a Michael reaction.

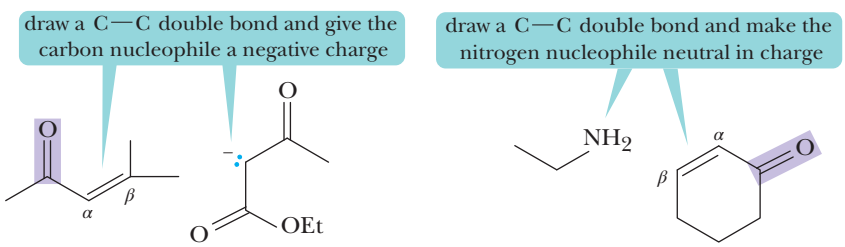
(a) Locate the carbonyl of the ketone, aldehyde, or ester and identify the α- and β-carbons. If there are multiple carbonyls, look for the β-carbon bonded to one of the nucleophiles presented in Table 15.2:



(b) Erase the bond between the β-carbon and the nucleophile:



(c) Draw a C—C double bond between the α- and β-carbons. The nucleophile should be drawn as negatively charged (in the case of carbon) or as a neutral amine (in the case of nitrogen).



EXAMPLE 15.11

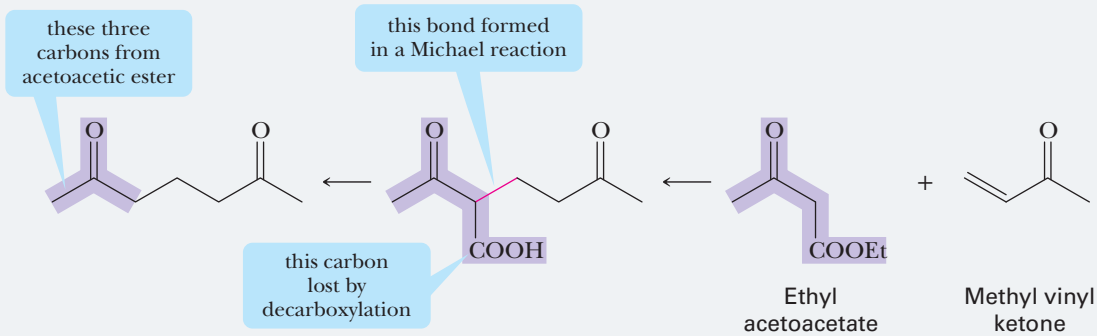
Show how the series of reactions in Example 15.10 and Problem 15.10 (Michael reaction, hydrolysis, acidification, and thermal decarboxylation) can be used to prepare 2,6-heptanedione.

STRATEGY

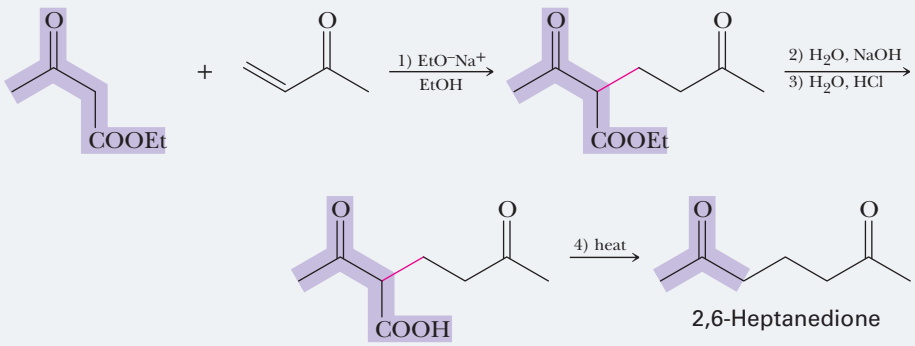
The key is to recognize that a COOH group beta to a ketone can be lost by decarboxylation. Once you find where that COOH group might have been located, you should see which carbons of the target molecule can be derived from the carbon skeleton of ethyl acetoacetate and which carbons can be derived from an α,β-unsaturated carbonyl compound.

SOLUTION

As shown here, the target molecule can be constructed from the carbon skeletons of ethyl acetoacetate and methyl vinyl ketone:



Following are the steps in their conversion to 2,6-heptanedione:



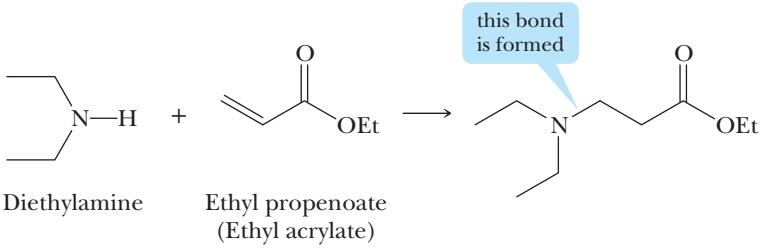
See problem 15.37

PROBLEM 15.11

Show how the sequence consisting of Michael reaction, hydrolysis, acidification, and thermal decarboxylation can be used to prepare pentanedioic acid (glutaric acid).

B. Michael Addition of Amines

As Table 15.2 shows, aliphatic amines also function as nucleophiles in Michael reactions. Diethylamine, for example, adds to methyl acrylate, as shown in the following equation:



EXAMPLE 15.12

Methylamine, CH_3NH_2, has two N—H bonds, and 1 mole of methylamine undergoes Michael reaction with 2 moles of ethyl acrylate. Draw a structural formula for the product of this double Michael reaction.

STRATEGY

Perform the first Michael reaction with 1 mole of ethyl acrylate. Then treat the product of that reaction with the second mole of ethyl acrylate.

SOLUTION

See problem 15.36

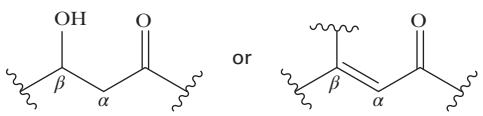
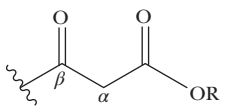
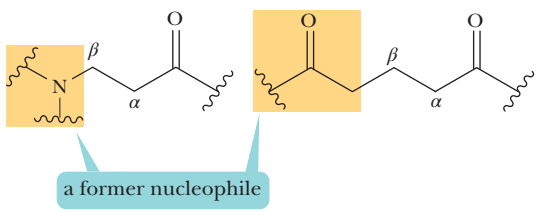
PROBLEM 15.12

The product of the double Michael reaction in Example 15.12 is a diester that, when treated with sodium ethoxide in ethanol, undergoes a Dieckmann condensation. Draw the structural formula for the product of this Dieckmann condensation followed by acidification with aqueous HCl.

HOW TO 15.4

Recognize the Products of Aldol, Claisen Condensation, and Michael Reactions

Aldol, Claisen condensation, and Michael reactions are some of the most important reactions in organic chemistry because they allow chemists to synthesize larger molecules from smaller, readily available compounds. The following table will help you to recognize when to use each reaction in a synthesis problem.

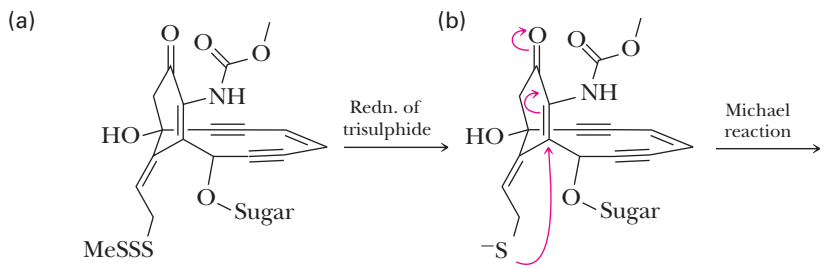
Reaction to Use	When This Substructure Is Needed in the Final Product	Example
Aldol reaction	β-hydroxy carbonyl or α,β-unsaturated carbonyl	
Claisen condensation	β-ketoester	
Michael reaction	β-substituted carbonyl	

Chemical Connections 15B

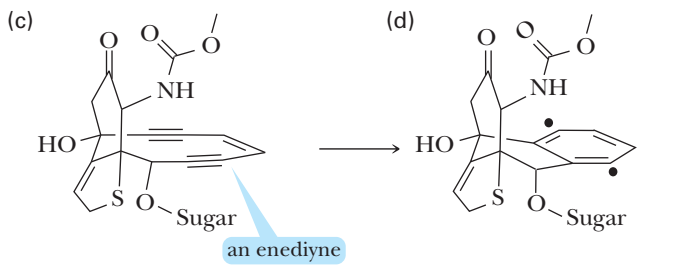
ANTITUMOR COMPOUNDS: THE MICHAEL REACTION IN NATURE

In 1987, a scientist happened upon a red rock (see photo) during a hike while vacationing in Texas. Thinking that there might be interesting chemicals within the organisms growing on the rock, the scientist brought the rock back to his laboratory at Wyeth (formerly Lederle Labs). It was subsequently found that a compound known as calicheamicin could be extracted from the bacteria *Micromonospora echinospora*, which was growing on the rock. The chemical turned out to be bioactive. After the compound's toxicity to cells was further researched, it was found to be among the most potent of all anticancer compounds. The mode of action of calicheamicin was elucidated, and the Michael reaction was found to play a crucial part in the mechanism for reactivity. In Step 1 of the mechanism, a trisulfide group on the molecule (a) is biochemically reduced to the anion of a thiol group. This, in turn, acts as a nucleophile and attacks the α,β-unsaturated ketone of the molecule (b). The product of this intramolecular Michael reaction (c) is thought to place great strain on the enediyne portion of calicheamicin, causing a rearrangement to occur that creates a benzene ring with two unpaired electrons (radicals) that are para to each other on the ring (d). This highly reactive structure acts to cleave both strands of DNA (Section 20.2B), which is the process that makes calicheamicin so damaging to tumor cells. By modifying the sugar unit of the calicheamicin so that it could be bonded to cancer-specific antibodies, this chemical, found by a curious chemist on vacation, has become a promising drug for cancer therapy.

K.C. Nicolaou, The Scripps Research Institute and University of California, San Diego



Abbreviated structure of calicheamicin



Benzene diradical (DNA cleaving agent)

Question

Provide a complete mechanism for the Michael reaction of b to produce c. Using fishhook arrows, provide a mechanism for the rearrangement of c to produce d.

SUMMARY OF KEY QUESTIONS

15.1 What Are Enolate Anions, and How Are They Formed?

- An **enolate anion** is an anion formed by the removal of an **α-hydrogen** from a carbonyl-containing compound.
- Aldehydes, ketones, and esters can be converted to their enolate anions by treatment with a metal alkoxide or other strong base.

15.2 What Is the Aldol Reaction?

- An **aldol reaction** is the addition of an enolate anion from one aldehyde or ketone to the carbonyl carbon of another aldehyde or ketone to form a **β-hydroxyaldehyde** or **β-hydroxyketone**.
- Dehydration of the product of an aldol reaction gives an **α,β-unsaturated aldehyde or ketone**.
- **Crossed aldol reactions** are useful only when appreciable differences in reactivity occur between the two carbonyl-containing compounds, such as when one of them has no α-hydrogens and can function only as an enolate anion acceptor.
- When both carbonyl groups are in the same molecule, aldol reaction results in the formation of a ring. These **intramolecular aldol reactions** are particularly useful for the formation of five- and six-membered rings.

15.3 What Are the Claisen and Dieckmann Condensations?

- A key step in the **Claisen condensation** is the addition of an enolate anion of one ester to a carbonyl group of another ester to form a tetrahedral carbonyl addition intermediate, followed by the collapse of the intermediate to give a β-ketoester.
- The **Dieckmann condensation** is an intramolecular Claisen condensation.

15.4 How Are Aldol Reactions and Claisen Condensations Involved in Biological Processes?

- **Acetyl-CoA** is the source of the carbon atoms for the synthesis of cholesterol, steroid hormones, and fatty acids. Various enzymes catalyze biological versions of aldol reactions and Claisen condensations during the syntheses of these compounds.
- Key intermediates in the synthesis of steroids and bile acids (Section 19.4) are mevalonic acid and isopentenyl pyrophosphate.

15.5 What Is the Michael Reaction?

- The **Michael reaction** is the addition of a nucleophile to a carbon–carbon double bond activated by an adjacent carbonyl group.
- The Michael reaction results in the formation of a new bond between the nucleophile and the β-carbon of an α,β-unsaturated carbonyl compound. The C—C double bond is converted to a C—C single bond in the reaction.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. All ketones and aldehydes with a carbon atom alpha to the carbonyl group can be converted to an enolate anion by treatment with a catalytic amount of base. (15.1)

2. A Dieckmann condensation favors seven- and eight-membered rings over four-, five-, and six-membered rings. (15.3)

3. An intramolecular aldol reaction favors five- and six-membered rings over four-, seven-, and eight-membered rings. (15.2)

4. A hydrogen that is alpha to two carbonyls is less acidic than a hydrogen that is alpha to only one carbonyl. (15.1)

5. The product of a Claisen condensation is a β-hydroxyester. (15.3)

6. The mechanism of a Michael reaction involves enol–keto tautomerization. (15.5)

7. An enolate anion can act as a nucleophile. (15.1)

8. An aldol reaction involves the reaction of an enolate anion with a ketone or an aldehyde. (15.2)

9. The product of an aldol reaction is a β-hydroxyester. (15.2)

10. Aldol reactions and Claisen condensations can be catalyzed by enzymes. (15.4)

11. A crossed aldol reaction is most effective when one of the carbonyl compounds is more reactive toward nucleophilic addition and cannot form an enolate anion. (15.2)

12. Hydrogen atoms alpha to a carbonyl are many times more acidic than vinyl or alkyl hydrogens. (15.1)

13. The Claisen condensation is a reaction between an enolate anion and an ester. (15.3)

14. The α-hydrogen of an ester is more acidic than the α-hydrogen of a ketone. (15.3)

15. An enolate anion is stabilized by resonance. (15.1)

16. All carbonyl compounds with an alpha hydrogen can be converted to an enolate anion by treatment with a catalytic amount of base. (15.1)

17. A crossed Claisen condensation is most effective when one of the carbonyl compounds can only function as an enolate anion acceptor. (15.3)

18. An enolate anion can participate in a Michael reaction. (15.5)

19. The product of an aldol reaction can be dehydrated to yield an α,β-unsaturated carbonyl compound. (15.2)

20. The Michael reaction is the reaction of a nucleophile with the β-carbon of an α,β-unsaturated carbonyl compound. (15.5)

21. An enolate anion can act as a base. (15.1)

22. The product of a Claisen condensation can be hydrolyzed and decarboxylated to form a ketone. (15.3)

23. An amine can participate in a Michael reaction. (15.5)

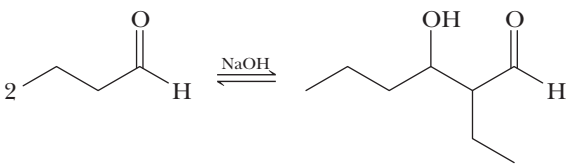
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) F (2) F (3) T (4) F (5) F (6) T (7) T (8) T (9) F (10) T
(11) T (12) T (13) T (14) F (15) T (16) F (17) T (18) T (19) T (20) T
(21) T (22) T (23) T

KEY REACTIONS

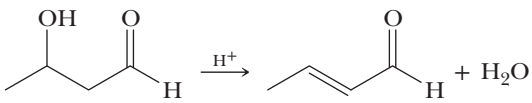
1. The Aldol Reaction (Section 15.2B)

The aldol reaction involves the nucleophilic addition of an enolate anion from one aldehyde or ketone to the carbonyl carbon of another aldehyde or ketone to give a β-hydroxyaldehyde or β-hydroxyketone:



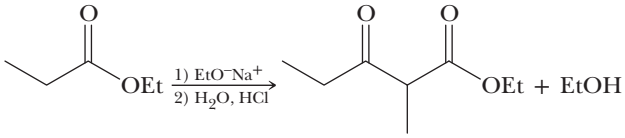
2. Dehydration of the Product of an Aldol Reaction (Section 15.2)

Dehydration of the β-hydroxyaldehyde or ketone from an aldol reaction occurs readily and gives an α,β-unsaturated aldehyde or ketone:



3. The Claisen Condensation (Section 15.3A)

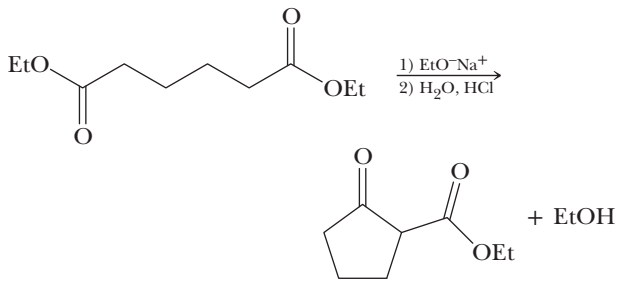
The product of a Claisen condensation is a β-ketoester:



Condensation occurs by nucleophilic acyl substitution in which the attacking nucleophile is the enolate anion of an ester.

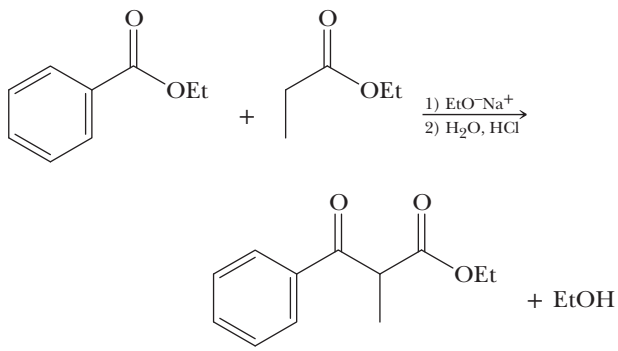
4. The Dieckmann Condensation (Section 15.3B)

An intramolecular Claisen condensation is called a Dieckmann condensation:



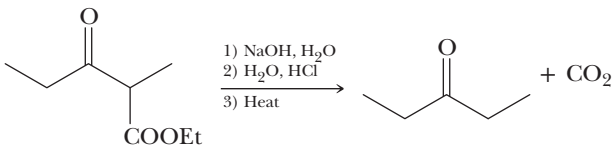
5. Crossed Claisen Condensations (Section 15.3C)

Crossed Claisen condensations are useful only when an appreciable difference exists in the reactivity between the two esters. Such is the case when an ester that has no α-hydrogens can function only as an enolate anion acceptor:



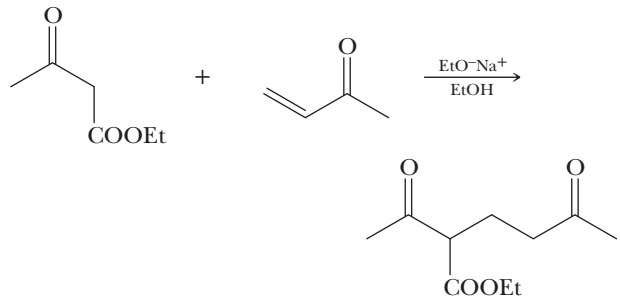
6. Hydrolysis and Decarboxylation of β-Ketoesters (Section 15.3D)

Hydrolysis of the ester, followed by decarboxylation of the resulting β-ketoacid, gives a ketone and carbon dioxide:



7. The Michael Reaction (Section 15.5)

Attack of a nucleophile at the β-carbon of an α,β-unsaturated carbonyl compound results in conjugate addition:

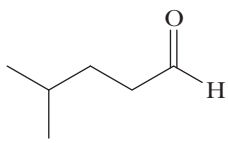


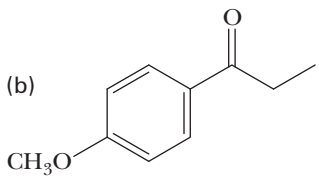
PROBLEMS

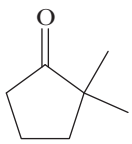
A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

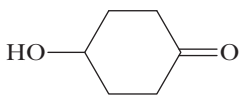
SECTIONS 15.1 AND 15.2 The Aldol Reaction

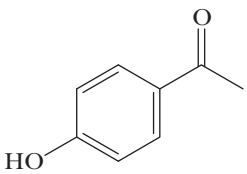
15.13 Identify the most acidic hydrogen(s) in each compound: **(See Example 15.1)**

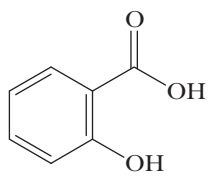
(a) 

(b) 

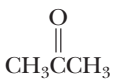
(c) 

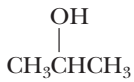
(d) 

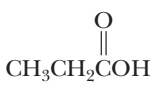
(e) 

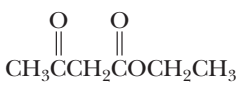
(f) 

15.14 Estimate the pK_a of each compound and arrange them in order of increasing acidity:

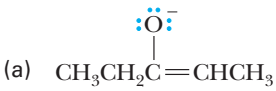
(a) 

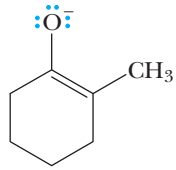
(b) 

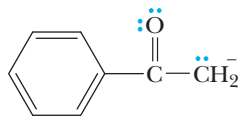
(c) 

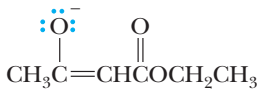
(d) 

15.15 Write a second contributing structure of each anion, and use curved arrows to show the redistribution of electrons that gives your second structure:

(a) 

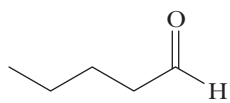
(b) 

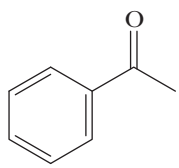
(c) 

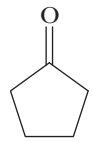
(d) 

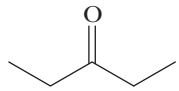
15.16 Treatment of 2-methylcyclohexanone with base gives two different enolate anions. Draw the contributing structure for each that places the negative charge on carbon.

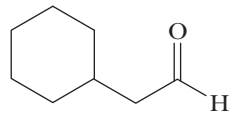
15.17 Draw a structural formula for the product of the aldol reaction of each compound and for the α,β-unsaturated aldehyde or ketone formed by dehydration of each aldol product: **(See Examples 15.2, 15.3)**

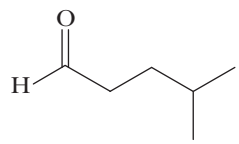
(a) 

(b) 

(c) 

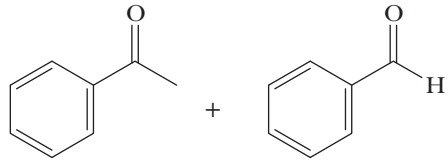
(d) 

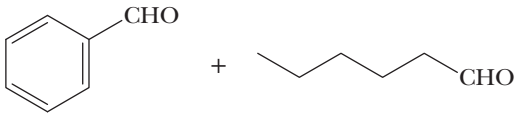
(e) 

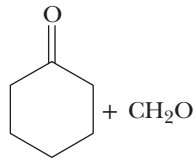
(f) 

15.18 Draw a structural formula for the product of each crossed aldol reaction and for the compound formed by dehydration of each aldol product: **(See Examples 15.3, 15.4)**

(a) $(CH_3)_3CCH + CH_3CCH_3$ (O over each C=O)

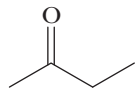
(b) 

(c) 

(d) 

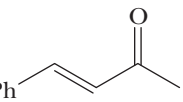
15.19 When a 1:1 mixture of acetone and 2-butanone is treated with base, six aldol products are possible. Draw a structural formula for each. **(See Example 15.4)**

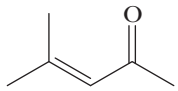
Acetone

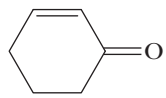


2-Butanone

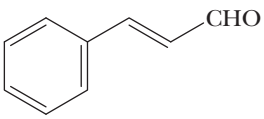
15.20 Show how to prepare each α,β-unsaturated ketone by an aldol reaction followed by dehydration of the aldol product: **(See Examples 15.2, 15.3)**

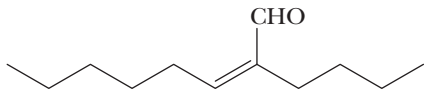
(a) 

(b) 

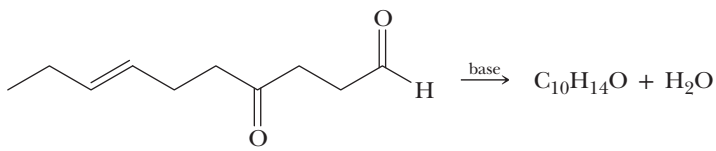
(c) 

15.21 Show how to prepare each α,β-unsaturated aldehyde by an aldol reaction followed by dehydration of the aldol product: **(See Examples 15.2, 15.3)**

(a) 

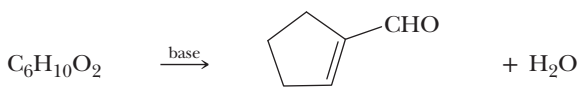
(b) 

15.22 When treated with base, the following compound undergoes an intramolecular aldol reaction, followed by dehydration, to give a product containing a ring (yield 78%): **(See Examples 15.3, 15.5)**



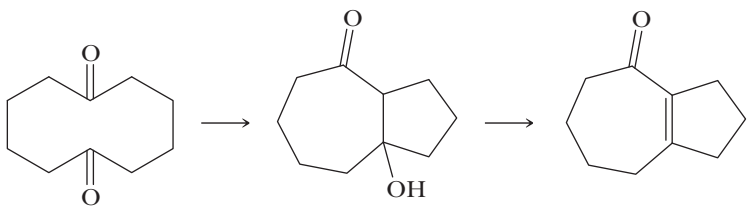
Propose a structural formula for this product.

15.23 Propose a structural formula for the compound with the molecular formula $C_6H_{10}O_2$ that undergoes an aldol reaction followed by dehydration to give this α,β-unsaturated aldehyde: **(See Examples 15.3, 15.5)**

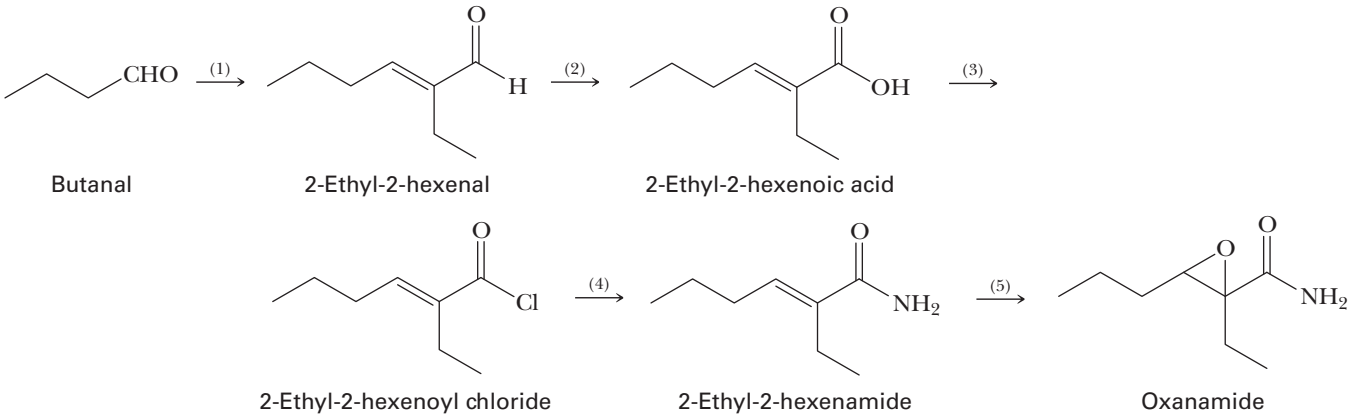


1-Cyclopentenecarbaldehyde

15.24 Show how to bring about this conversion: **(See Examples 15.3, 15.5)**



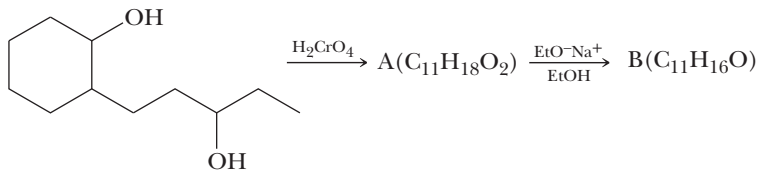
***15.25** Oxanamide, a mild sedative, is synthesized from butanal in these five steps:



(a) Show reagents and experimental conditions that might be used to bring about each step in this synthesis.

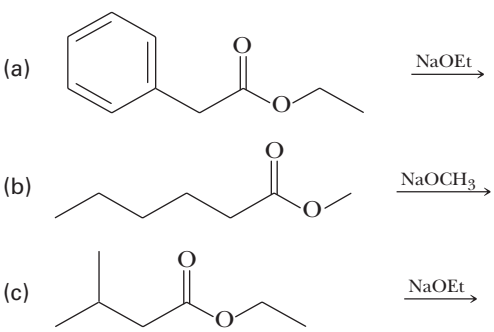
(b) How many stereocenters are in oxanamide? How many stereoisomers are possible for oxanamide?

15.26 Propose structural formulas for compounds A and B:



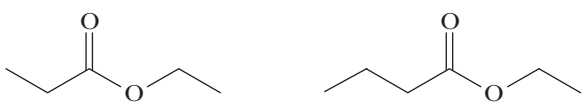
SECTION 15.3 The Claisen and Dieckmann Condensations

15.27 Show the product of the Claisen condensation of each ester: **(See Example 15.6)**

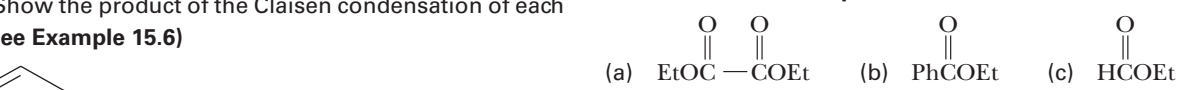


15.28 Draw a structural formula for the product of saponification, acidification, and decarboxylation of each β-ketoester formed in Problem 15.27. **(See Example 15.9)**

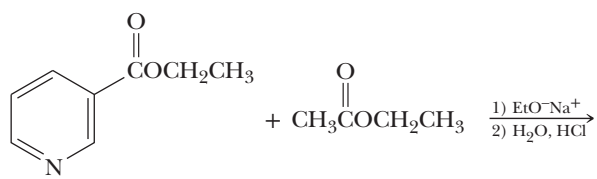
15.29 When a 1:1 mixture of ethyl propanoate and ethyl butanoate is treated with sodium ethoxide, four Claisen condensation products are possible. Draw a structural formula for each product. **(See Example 15.8)**



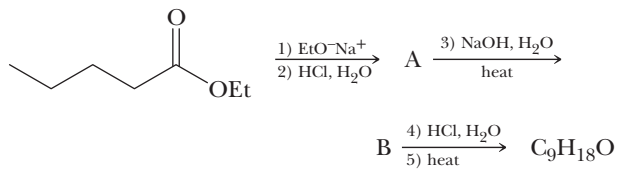
15.30 Draw a structural formula for the β-ketoester formed in the crossed Claisen condensation of ethyl propanoate with each ester: **(See Example 15.8)**



15.31 Complete the equation for this crossed Claisen condensation: **(See Example 15.8)**

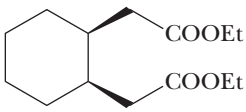


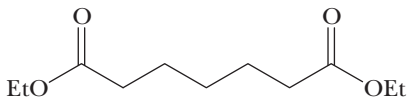
15.32 The Claisen condensation can be used as one step in the synthesis of ketones, as illustrated by this reaction sequence: **(See Example 15.9)**



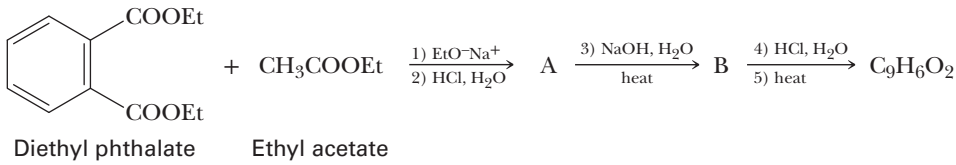
Propose structural formulas for compounds A, B, and the ketone formed in the sequence.

15.33 Draw a structural formula for the product of treating each diester with sodium ethoxide followed by acidification with HCl (*Hint:* These are Dieckmann condensations): **(See Example 15.7)**

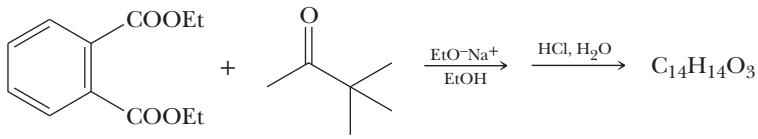
(a) 

(b) 

15.34 Claisen condensation between diethyl phthalate and ethyl acetate, followed by saponification, acidification, and decarboxylation, forms a diketone, $C_9H_6O_2$. Propose structural formulas for compounds A, B, and the diketone: **(See Example 15.9)**



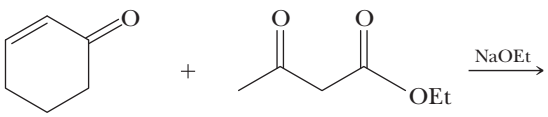
***15.35** The rodenticide and insecticide pindone is synthesized by the following sequence of reactions: **(See Example 15.10)**

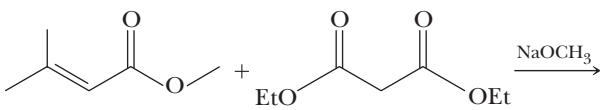


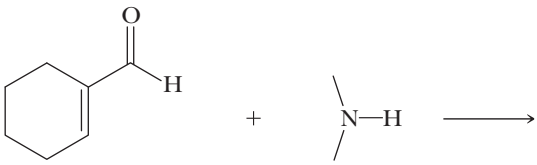
Propose a structural formula for pindone.

SECTION 15.5 The Michael Reaction

15.36 Show the product of the Michael reaction of each α,β-unsaturated carbonyl compound: **(See Examples 15.10, 15.12)**

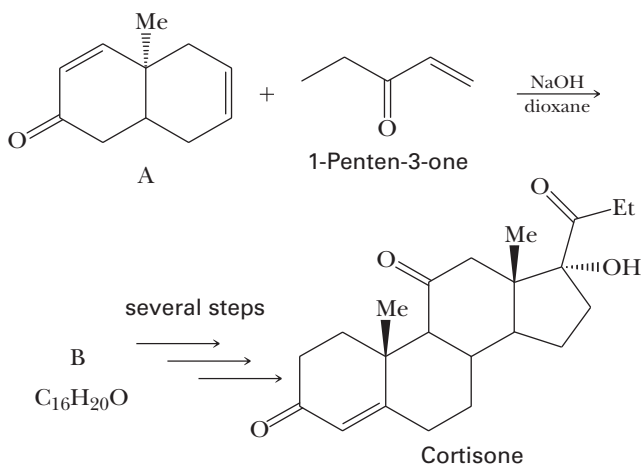
(a) 

(b) 

(c) 

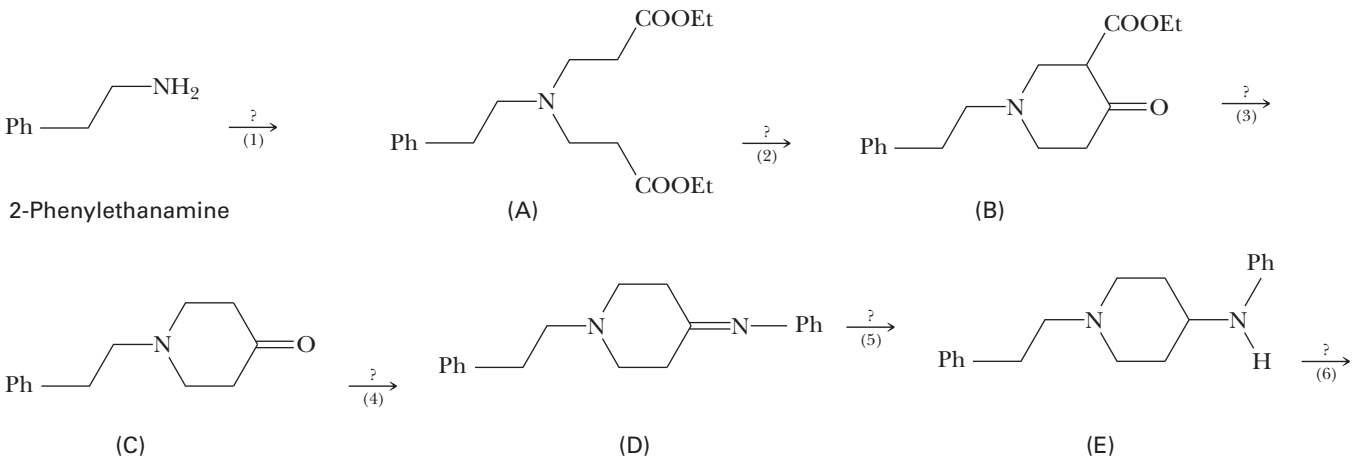
***15.37** Show the outcomes of subjecting the Michael reaction products in Problems 15.36a and 15.36b to hydrolysis, followed by acidification, followed by thermal decarboxylation. **(See Example 15.11)**

***15.38** The classic synthesis of the steroid cortisone, a drug used to treat some types of allergies, involves a Michael reaction in which 1-penten-3-one and compound A are treated with NaOH in the solvent dioxane. Provide a structure for B, the product of this reaction.



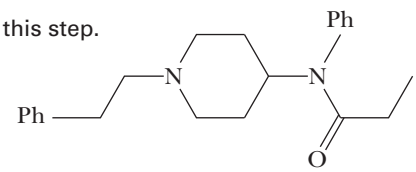
Synthesis

***15.39** Fentanyl is a nonopoid (nonmorphinelike) analgesic used for the relief of severe pain. It is approximately 50 times more potent in humans than morphine itself. One synthesis for fentanyl begins with 2-phenylethanamine:



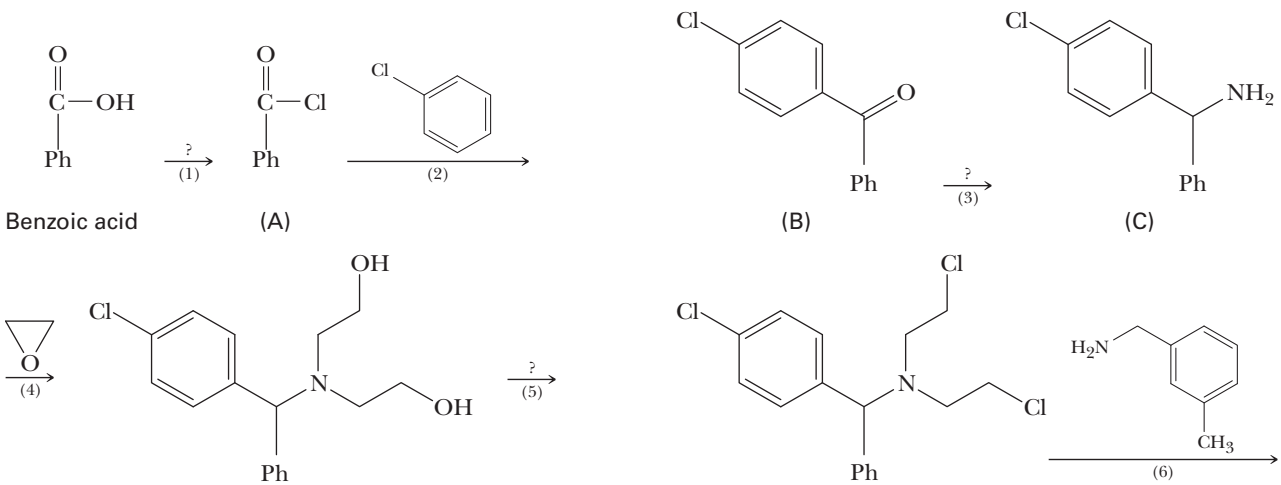
2-Phenylethanamine (A) (B) (C) (D) (E)

(a) Propose a reagent for Step 1. Name the type of reaction that occurs in this step.
(b) Propose a reagent to bring about Step 2. Name the type of reaction that occurs in this step.
(c) Propose a series of reagents that will bring about Step 3.
(d) Propose a reagent for Step 4. Identify the imine (Schiff base) part of Compound D.
(e) Propose a reagent to bring about Step 5.
(f) Propose two different reagents, either of which will bring about Step 6.
(g) Is fentanyl chiral? Explain.



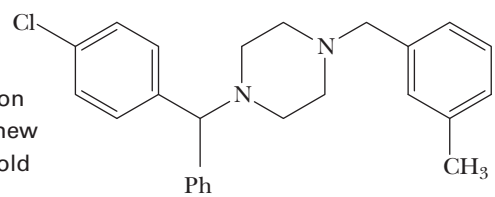
Fentanyl

***15.40** Meclizine is an antiemetic. (It helps prevent or at least lessen the vomiting associated with motion sickness, including seasickness.) Among the names of the over-the-counter preparations of meclizine are Bonine®, Sea-Legs®, Antivert®, and Navicalm®. Meclizine can be produced by the following series of reactions:



Benzoic acid (A) (B) (C) (D) (E)

(a) Name the functional group in (A). What reagent is most commonly used to convert a carboxyl group to this functional group?
(b) The catalyst for Step 2 is aluminum chloride, $AlCl_3$. Name the type of reaction that occurs in this step. The product shown here has the orientation of the new group para to the chlorine atom of chlorobenzene. Suppose you were not told the orientation of the new group. Would you have predicted it to be ortho, meta, or para to the chlorine atom? Explain.



Meclizine

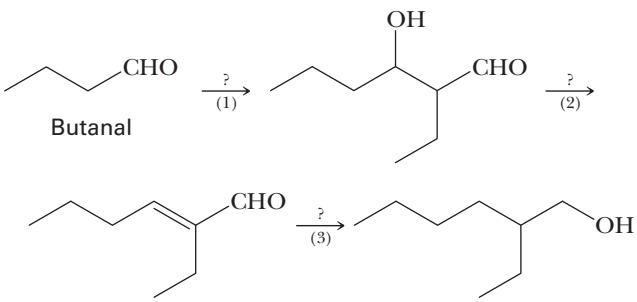
(c) What set of reagents can be used in Step 3 to convert the C═O group to an —NH_2 group?

(d) The reagent used in Step 4 is the cyclic ether ethylene oxide. Most ethers are quite unreactive to nucleophiles such as the 1° amine in this step. Ethylene oxide, however, is an exception to this generalization. What is it about ethylene oxide that makes it so reactive toward ring-opening reactions with nucleophiles?

(e) What reagent can be used in Step 5 to convert each 1° alcohol to a 1° halide?

(f) Step 6 is a double nucleophilic displacement. Which mechanism is more likely for this reaction, S_N1 or S_N2? Explain.

***15.41** 2-Ethyl-1-hexanol is used for the synthesis of the sunscreen octyl *p*-methoxycinnamate. (See Chemical Connections 14A.) This primary alcohol can be synthesized from butanal by the following series of steps:



Butanal

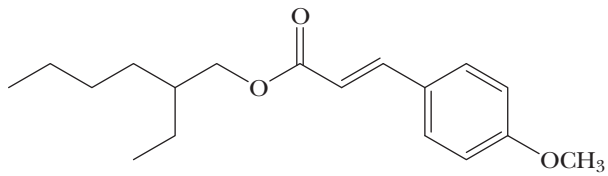
2-Ethyl-1-hexanol

(a) Propose a reagent to bring about Step 1. What name is given to this type of reaction?

(b) Propose a reagent for Step 2.

(c) Propose a reagent for Step 3.

(d) Following is a structural formula for the commercial sunscreening ingredient:

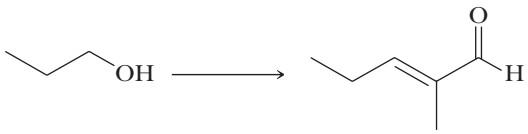


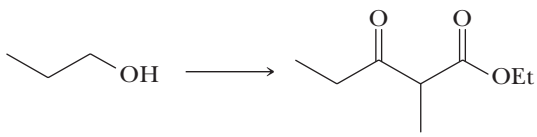
Octyl *p*-methoxycinnamate

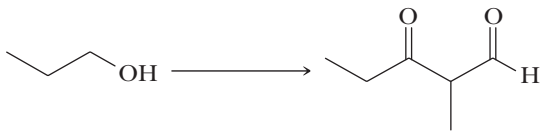
What carboxylic acid and alcohol would you use to form this ester? How would you bring about the esterification reaction?

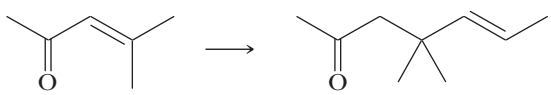
CHEMICAL TRANSFORMATIONS

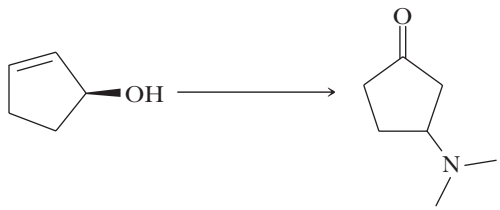
15.42 Test your cumulative knowledge of the reactions learned thus far by completing the following chemical transformations. *Note:* Most will require more than one step.

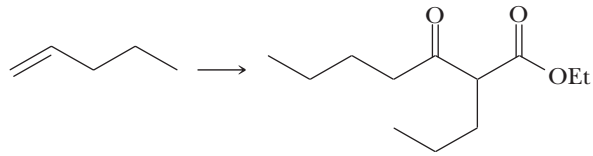
(a) 

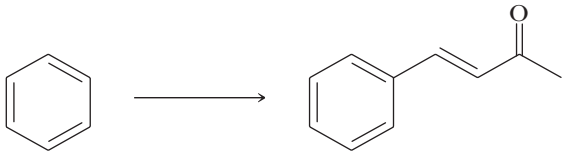
(b) 

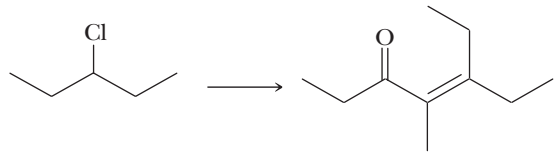
(c) 

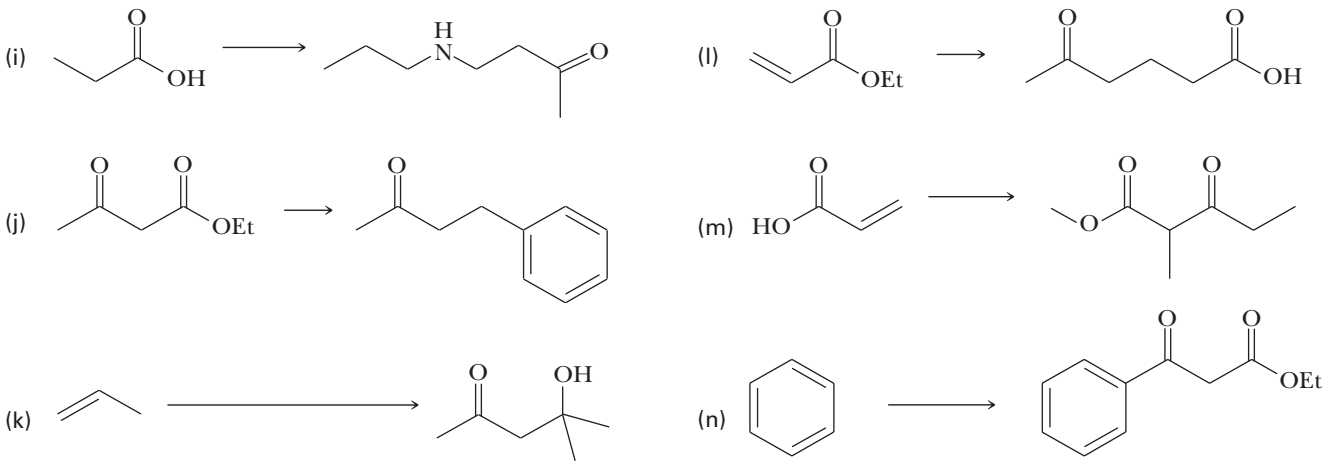
(d) 

(e) 

(f) 

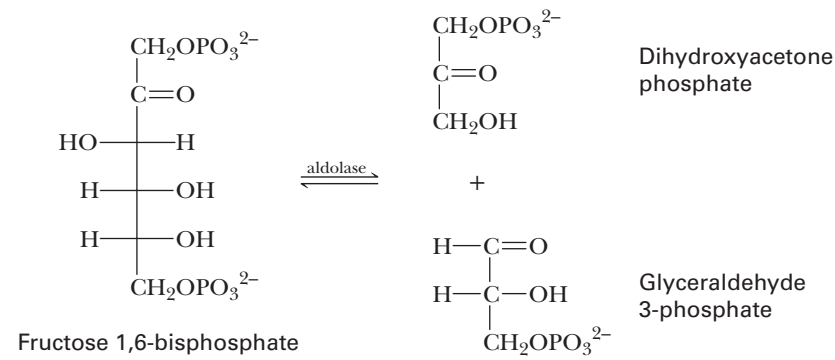
(g) 

(h) 



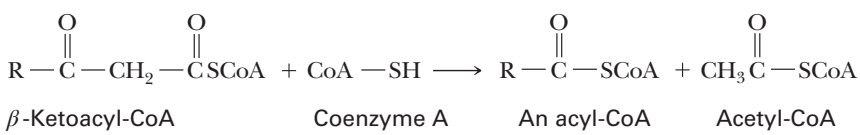
LOOKING AHEAD

***15.43** The following reaction is one of the 10 steps in glycolysis, a series of enzyme-catalyzed reactions by which glucose is oxidized to two molecules of pyruvate:



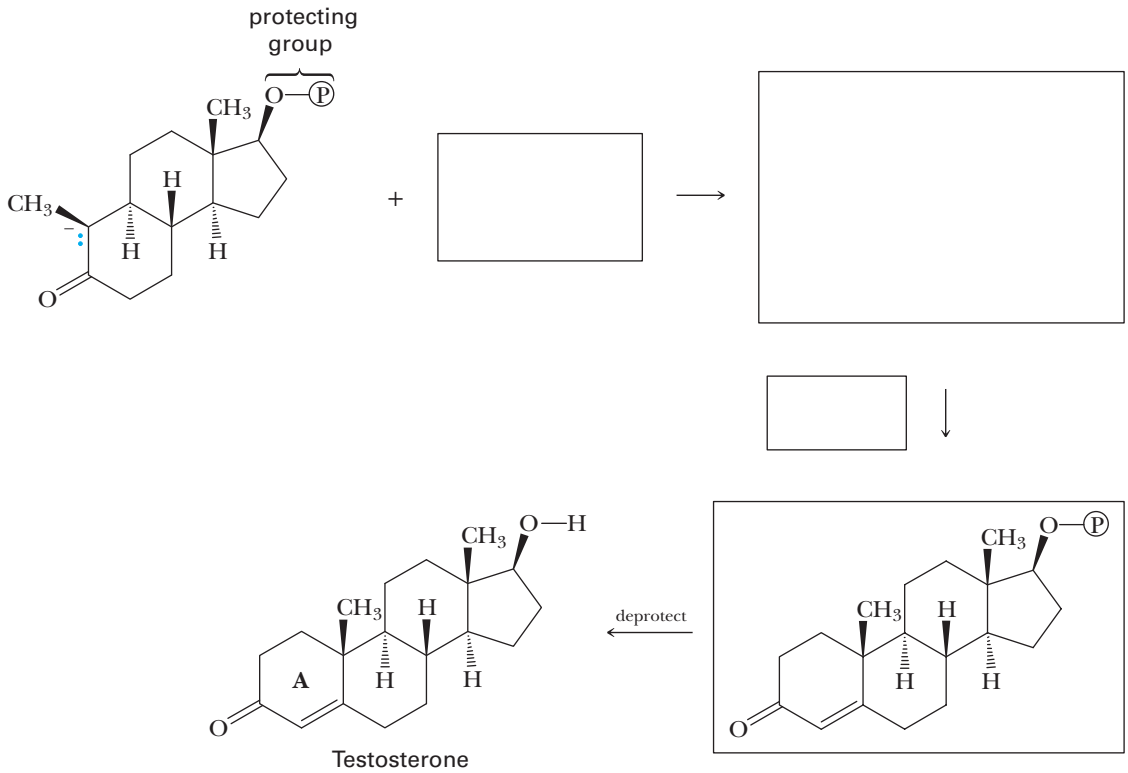
Show that this step is the reverse of an aldol reaction.

***15.44** The following reaction is the fourth in the set of four enzyme-catalyzed steps by which the hydrocarbon chain of a fatty acid is oxidized, two carbons at a time, to acetyl-coenzyme A:



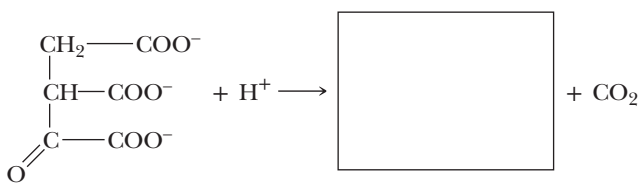
Show that this reaction is the reverse of a Claisen condensation.

***15.45** Steroids are a major type of lipid (Section 19.4) with a characteristic tetracyclic ring system. Show how the **A** ring of the steroid testosterone can be constructed from the indicated precursors, using a Michael reaction followed by an aldol reaction (with dehydration):



Testosterone

***15.46** The third step of the citric acid cycle involves the protonation of one of the carboxylate groups of oxalosuccinate, a β-ketoacid, followed by decarboxylation to form α-ketoglutarate:



Oxalosuccinate α-Ketoglutarate

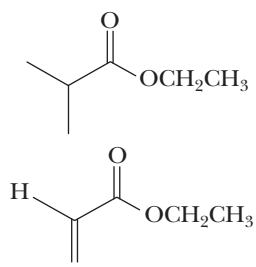
Write the structural formula of α-ketoglutarate.

GROUP LEARNING ACTIVITIES

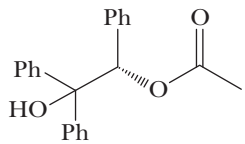
15.47 Nitroethane has a pK_a of 8.5, which makes it slightly more acidic than ethyl acetoacetate. Acetonitrile has a pK_a of 25, which makes it comparable in acidity to most esters. Account for the acidities of nitroethane and acetonitrile. As a group, decide whether the conjugate bases of these compounds could act similarly to enolates by drawing examples of such reactions.

$CH_3—CH_2—NO_2$ Nitroethane $CH_3—C\equiv N$ Acetonitrile

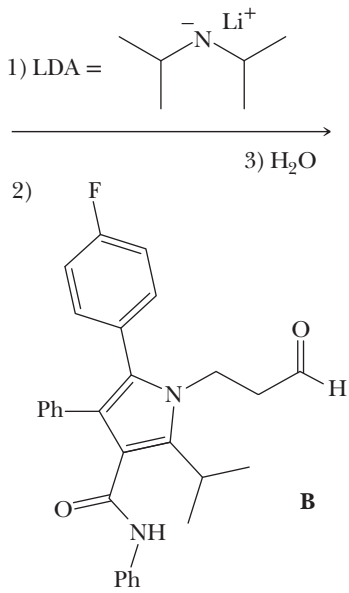
15.48 As a group, discuss why the two compounds shown do not undergo self-Claisen condensation reactions. Refer to Section 15.3D if needed.



15.49 One synthesis of atorvastatin, the common drug sold under the trade name Lipitor® and used to treat high cholesterol, involves the generation of an enolate from **A** followed by reaction with the fluorinated compound **B.** The enolate is generated quantitatively by reaction with lithium diisopropylamide (LDA), a very strong nitrogenous base. As a group, predict the product of the reaction of the enolate of **A** with **B** and provide a mechanism for the reaction. Also, debate why LDA preferentially forms the enolate rather than reacting with the more acidic alcohol proton in **A**.

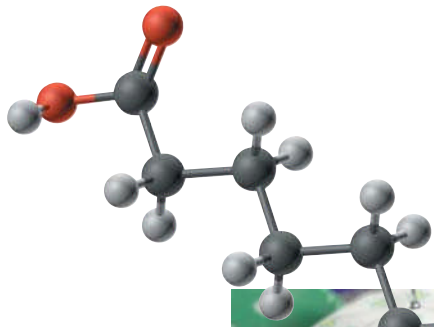


A



B

Organic Polymer Chemistry



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16

A sea of umbrellas on a rainy day. Inset: A model of adipic acid, one of the two compounds from which nylon 66 is made.

KEY QUESTIONS

CHEMICAL CONNECTIONS

THE TECHNOLOGICAL ADVANCEMENT of any society is inextricably tied to the materials available to it. Indeed, historians have used the emergence of new materials as a way of establishing a time line to mark the development of human civilization (e.g., Stone Age, Bronze Age, and Iron Age). As part of the search to discover new materials, scientists have made increasing use of organic chemistry for the preparation of synthetic materials known as polymers. The versatility afforded by these polymers allows for the creation and fabrication of materials with ranges of properties unattainable using such materials as wood, metals, and ceramics. Deceptively simple changes in the chemical structure of a given polymer, for example, can change its mechanical properties from those of a sandwich bag to those of a bulletproof vest. Furthermore, structural changes can introduce properties never before imagined in organic polymers. For instance, using well-defined organic reactions, chemists can turn one type of polymer into an insulator (e.g., the rubber sheath that surrounds electrical cords). Treated differently, the same type of polymer can be made into an electrical conductor with a conductivity nearly equal to that of metallic copper!

The years since the 1930s have seen extensive research and development in organic polymer chemistry, and an almost explosive growth in plastics, coatings, and rubber technology has created a worldwide multibillion-dollar industry. A few basic characteristics account for this phenomenal growth. First, the raw materials for synthetic polymers are derived mainly

from petroleum. With the development of petroleum-refining processes, raw materials for the synthesis of polymers became generally cheap and plentiful. Second, within broad limits, scientists have learned how to tailor polymers to the requirements of the end use. Third, many consumer products can be fabricated more cheaply from synthetic polymers than from such competing materials as wood, ceramics, and metals. For example, polymer technology created the water-based (latex) paints that have revolutionized the coatings industry, and plastic films and foams have done the same for the packaging industry. The list could go on and on as we think of the manufactured items that are everywhere around us in our daily lives.

16.1 What Is the Architecture of Polymers?

Polymers (Greek: *poly* + *meros*, many parts) are long-chain molecules synthesized by linking **monomers** (Greek: *mono* + *meros*, single part) through chemical reactions. The molecular weights of polymers are generally high compared with those of common organic compounds and typically range from 10,000 g/mol to more than 1,000,000 g/mol. The architectures of these macromolecules can also be quite diverse: There are polymer architectures with linear and branched chains, as well as those with comb, ladder, and star structures (Figure 16.1). Additional structural variations can be achieved by introducing covalent cross-links between individual polymer chains.

In polymer chemistry, the term **plastic** refers to any polymer that can be molded when hot and that retains its shape when cooled. **Thermoplastics** are polymers which, when melted, become sufficiently fluid that they can be molded into shapes that are retained when they are cooled. **Thermosetting plastics**, or thermosets, can be molded when they are first prepared, but once cooled, they harden irreversibly and cannot be remelted. Because of their very different physical characteristics, thermoplastics and thermosets must be processed differently and are used in very different applications.

The single most important property of polymers at the molecular level is the size and shape of their chains. Shorter chains tend to form softer and more brittle materials, while longer chains form stronger and more flexible materials. These vastly different properties arise directly from the difference in size and molecular architecture of the individual polymer chains.

Polymer From the Greek *poly*, many and *meros*, parts; any long-chain molecule synthesized by linking together many single parts called monomers.

Monomer From the Greek *mono*, single and *meros*, part; the simplest nonredundant unit from which a polymer is synthesized.

Plastic A polymer that can be molded when hot and retains its shape when cooled.

Thermoplastic A polymer that can be melted and molded into a shape that is retained when it is cooled.

Thermosetting plastic A polymer that can be molded when it is first prepared, but, once cooled, hardens irreversibly and cannot be remelted.

16.2 How Do We Name and Show the Structure of a Polymer?

We typically show the structure of a polymer by placing parentheses around the **repeating unit**, which is the smallest molecular fragment that contains all the structural features of the chain. A subscript n placed outside the parentheses indicates that the unit repeats n times. Thus, we can reproduce the structure of an entire polymer chain by repeating the enclosed

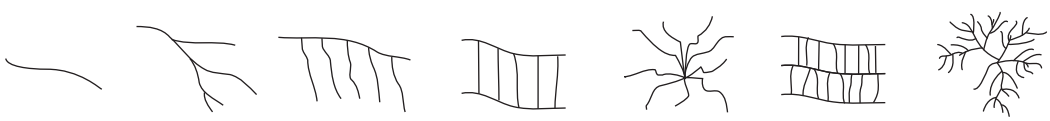
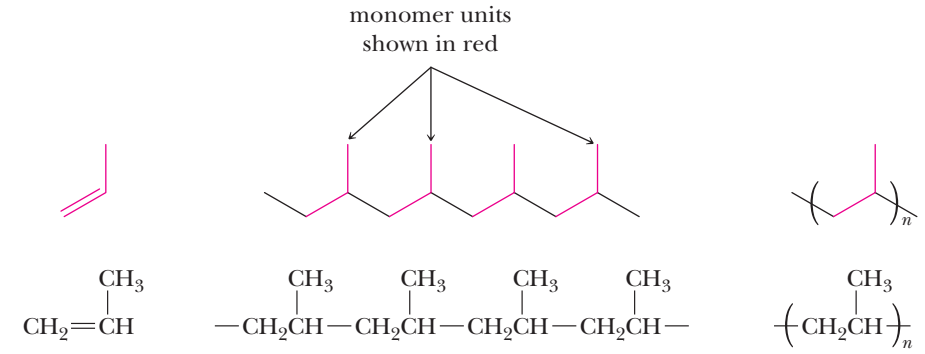


FIGURE 16.1 Various polymer architectures. Each line represents organic chains of covalently bonded atoms.

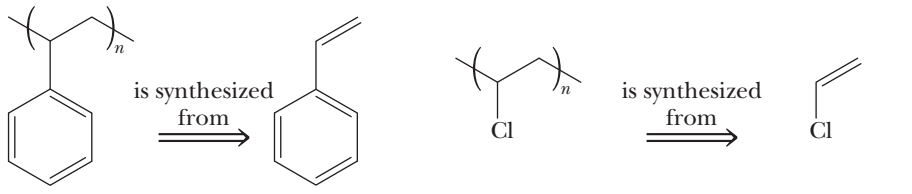
Average degree of polymerization, *n* A subscript placed outside the parentheses of the simplest nonredundant unit of a polymer to indicate that the unit repeats *n* times in the polymer.

structure in both directions. An example is polypropylene, which is derived from the polymerization of propylene:



The monomer (propylene) | Part of an extended chain of polypropylene | The repeating unit of polypropylene

The most common method of naming a polymer is to add the prefix **poly-** to the name of the monomer from which the polymer is synthesized. Examples are polyethylene and polystyrene. In the case of a more complex monomer or when the name of the monomer is more than one word (e.g., the monomer vinyl chloride), parentheses are used to enclose the name of the monomer:



Polystyrene | Styrene | Poly(vinyl chloride) (PVC) | Vinyl chloride

EXAMPLE 16.1

Given the following structure, determine the polymer's repeating unit; redraw the structure, using the simplified parenthetical notation; and name the polymer. Assume that the monomer unit is an alkene:

(repeating unit in red)

STRATEGY

Identify the repeating structural unit of the chain and place parentheses around it. Add the subscript *n* to indicate that this unit repeats *n* times.

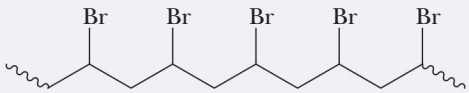
SOLUTION

The repeating unit is $—CH_2CF_2—$ and the polymer is written $+CH_2CF_2+_n$. The repeat unit is derived from 1,1-difluoroethylene and the polymer is named poly(1,1-difluoroethylene). This polymer is used in microphone diaphragms.

See problems 16.9, 16.10

PROBLEM 16.1

Given the following structure, determine the polymer's repeat unit; redraw the structure, using the simplified parenthetical notation; and name the polymer:

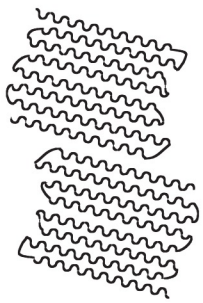


16.3 What Is Polymer Morphology? Crystalline versus Amorphous Materials

Polymers, like small organic molecules, tend to crystallize upon precipitation or as they are cooled from a melt. Acting to inhibit this tendency is the very large size of their molecules, which tends to inhibit diffusion, and their sometimes complicated or irregular structures, which prevent efficient packing of their chains. The result is that polymers in the solid state tend to be composed of both ordered **crystalline domains** (crystallites) and disordered **amorphous domains** (Figure 16.2). The relative amounts of crystalline and amorphous domains differ from polymer to polymer and frequently depend on the manner in which the material is processed (Figure 16.3). We often find high degrees of crystallinity in polymers with regular, compact structures and strong intermolecular forces, such as hydrogen bonding.

Crystalline domains Ordered crystalline regions in the solid state of a polymer; also called crystallites.

Amorphous domains Disordered, noncrystalline regions in the solid state of a polymer.



Arrangement of crystalline polymer chains

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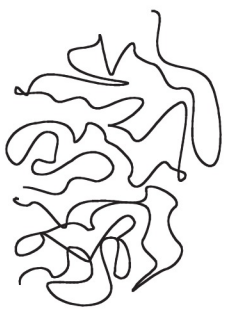
Case made of polyethylene, a crystalline polymer



Arrangement of amorphous polymer chains

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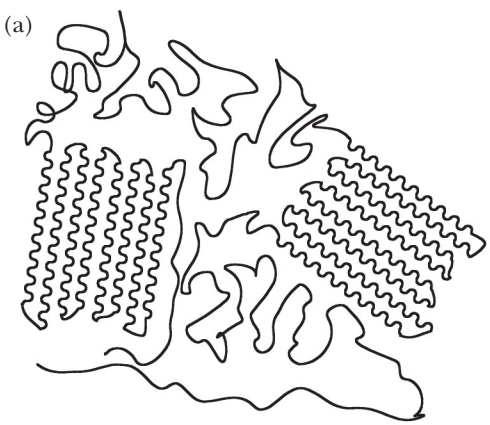
Rubber bands made of latex rubber, an amorphous polymer

FIGURE 16.2 Examples of various polymer morphologies.



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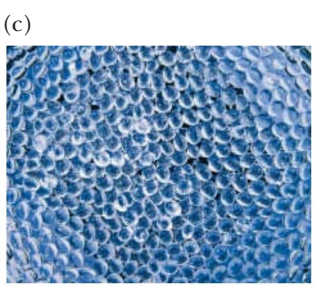

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FIGURE 16.3 (a) Example of a polymer chain with both crystalline and amorphous domains, (b) a polymer with a greater percentage of crystalline domains is less transparent than (c) a polymer with a greater percentage of amorphous domains.

Amorphous domains have little or no long-range order. Highly amorphous polymers are sometimes referred to as **glassy** polymers. Because they lack crystalline domains that scatter light, amorphous polymers are transparent. In addition, they are typically weak polymers, in terms of both their high flexibility and their low mechanical strength. On being heated, amorphous polymers are transformed from a hard, glassy state to a soft, flexible, rubbery state. The temperature at which this transition occurs is called the **glass transition temperature (T_g)**. Amorphous polystyrene, for example, has a $T_g = 100°C$. At room temperature, it is a rigid solid used for drinking cups, foamed packaging materials, disposable medical wares, tape reels, and so forth. If it is placed in boiling water, it becomes soft and rubbery.

Elastomer A material that, when stretched or otherwise distorted, returns to its original shape when the distorting force is released.

Rubber materials must have low T_g values in order to behave as **elastomers (elastic polymers)**. If the temperature drops below its T_g value, then the material is converted to a rigid glassy solid and all elastomeric properties are lost. A poor understanding of this behavior of elastomers contributed to the *Challenger* spacecraft disaster in 1985. The elastomeric O-rings used to seal the solid booster rockets had a T_g value around 0 °C. When the temperature dropped to an unanticipated low on the morning of the launch of the craft, the O-ring seals dropped below their T_g value and obediently changed from elastomers to rigid glasses, losing any sealing capabilities. The rest is tragic history. The physicist Richard Feynman sorted this out publicly in a famous televised hearing in which he put a *Challenger*-type O-ring in ice water and showed that its elasticity was lost!

16.4 What Is Step-Growth Polymerization?

Step-growth polymerization A polymerization in which chain growth occurs in a stepwise manner between difunctional monomers, for example, between adipic acid and hexamethylenediamine to form Nylon 66. Also referred to as condensation polymerization.

Polymerizations in which chain growth occurs in a stepwise manner are called **step-growth polymerization** or **condensation polymerizations**. Step-growth polymers are formed by reaction between difunctional molecules, with each new bond created in a separate step. During polymerization, monomers react to form dimers, dimers react with monomers to form trimers, dimers react with dimers to form tetramers, and so on.

There are two common types of step-growth processes: (1) reaction between A—M—A and B—M—B type monomers to give $\text{-(-A—M—A—B—M—B-)-}_n$ polymers and (2) the self-condensation of A—M—B monomers to give -(-A—M—B-)-_n polymers. In this notation, "M" indicates the monomer and "A" and "B" the reactive functional groups on the monomer. In each type of step-growth polymerization, an A functional group reacts exclusively with a B functional group, and a B functional group reacts exclusively with an A functional group. New covalent bonds in step-growth polymerizations are generally formed by polar reactions between A and B functional groups—for example, nucleophilic acyl substitution. In this section, we discuss five types of step-growth polymers: polyamides, polyesters, polycarbonates, polyurethanes, and epoxy resins.

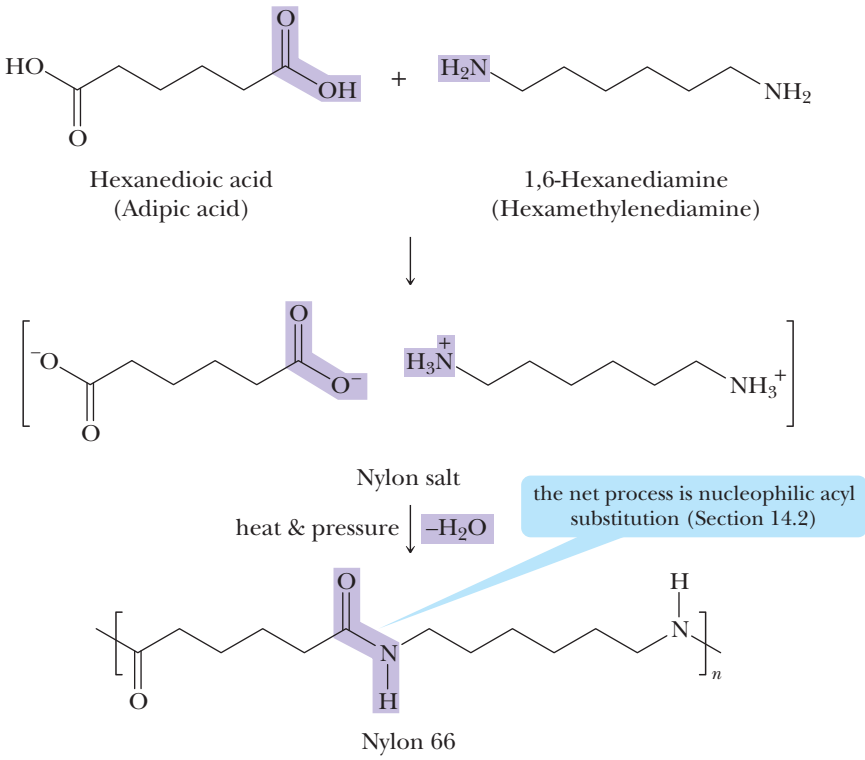
A. Polyamides

Polyamide A polymer in which each monomer unit is joined to the next by an amide bond, as for example Nylon 66.

In the early 1930s, chemists at E. I. DuPont de Nemours & Company began fundamental research into the reactions between dicarboxylic acids and diamines to form **polyamides**. In 1934, they synthesized the first purely synthetic fiber, nylon 66, so named because it is synthesized from two different monomers, each containing six carbon atoms.

Autoclave An instrument used to sterilize items by subjecting them to steam and high pressure.

In the synthesis of nylon 66, hexanedioic acid and 1,6-hexanediamine are dissolved in aqueous ethanol, in which they react to form a one-to-one salt called nylon salt. This salt is then heated in an **autoclave** to 250 °C and an internal pressure of 15 atm. Under these extreme conditions, $—COO^-$ groups from the dicarboxylic acid and $—NH_3^+$ groups from the diamine react by the loss of H_2O to form a polyamide. Nylon 66 formed under these conditions melts at 250 to 260 °C and has a molecular weight ranging from 10,000 to 20,000 g/mol:



In the first stage of fiber production, crude nylon 66 is melted, spun into fibers, and cooled. Next, the melt-spun fibers are **cold drawn** (drawn at room temperature) to about four times their original length to increase their degree of crystallinity. As the fibers are drawn, individual polymer molecules become oriented in the direction of the fiber axis, and hydrogen bonds form between carbonyl oxygens of one chain and amide hydrogens of another chain (Figure 16.4). The effects of the orientation of polyamide molecules on the physical properties of the fiber are dramatic—both tensile strength and stiffness are increased markedly. Cold drawing is an important step in the production of most synthetic fibers.

The nylons are a family of polymers, the members of which have subtly different properties that suit them to one use or another. The two most widely used members of the family are nylon 66 and nylon 6. Nylon 6 is so named because it is synthesized from caprolactam,

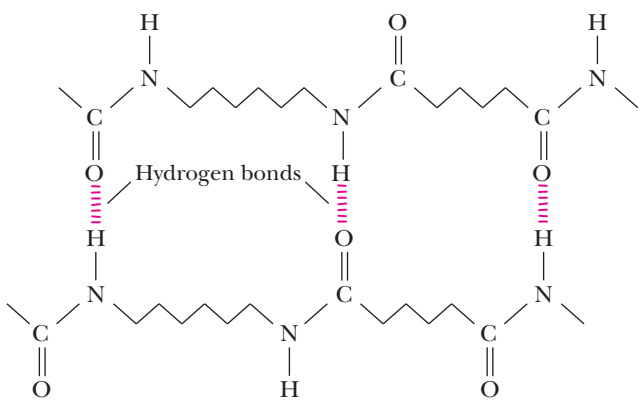
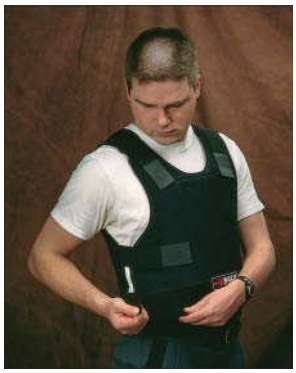


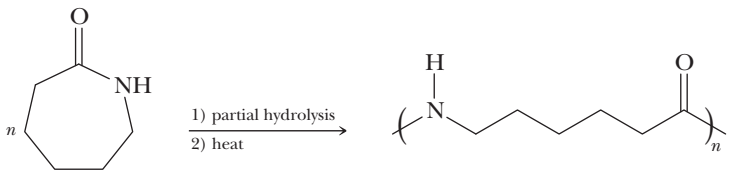
FIGURE 16.4 The structure of cold-drawn nylon 66. Hydrogen bonds between adjacent polymer chains provide additional tensile strength and stiffness to the fibers.



Charles D. Winters

Bulletproof vests have a thick layer of Kevlar.

a six-carbon monomer. In this synthesis, caprolactam is partially hydrolyzed to 6-aminohexanoic acid and then heated to 250 °C to bring about polymerization:

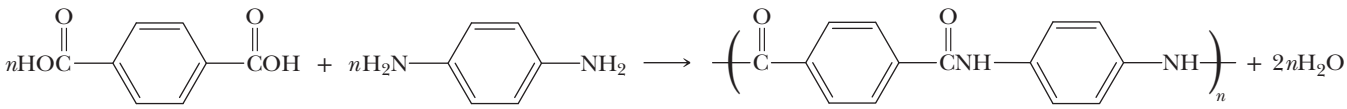


Caprolactam — Nylon 6

Nylon 6 is fabricated into fibers, bristles, rope, high-impact moldings, and tire cords.

Aramid A polyaromatic *amide*; a polymer in which the monomer units are an aromatic diamine and an aromatic dicarboxylic acid.

Based on extensive research into the relationships between molecular structure and bulk physical properties, scientists at DuPont reasoned that a polyamide containing aromatic rings would be stiffer and stronger than either nylon 66 or nylon 6. In early 1960, DuPont introduced Kevlar, a polyaromatic amide (**aramid**) fiber synthesized from terephthalic acid and *p*-phenylenediamine:



1,4-Benzenedicarboxylic acid (Terephthalic acid) — 1,4-Benzenediamine (*p*-Phenylenediamine) — Kevlar

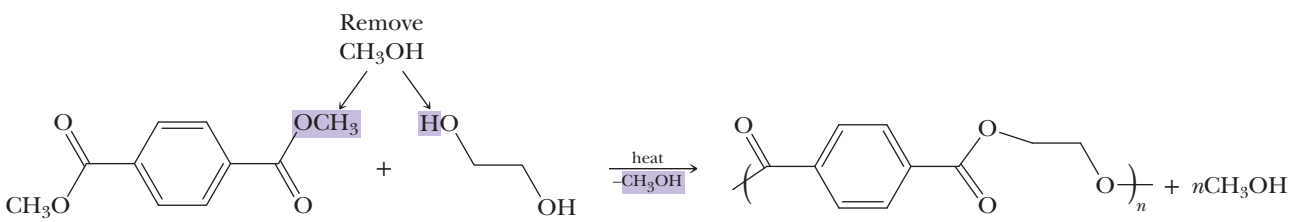
Ken Karp for John WIley & Sons

Because Mylar film has smaller pores than latex film, it is used for balloons that last longer when inflated with helium; the helium atoms diffuse only slowly through the pores of the film.

One of the remarkable features of Kevlar is its light weight compared with that of other materials of similar strength. For example, a 7.6-cm (3-in.) cable woven of Kevlar has a strength equal to that of a similarly woven 7.6-cm (3-in.) steel cable. However, whereas the steel cable weighs about 30 kg/m (20 lb/ft), the Kevlar cable weighs only 6 kg/m (4 lb/ft). Kevlar now finds use in such articles as anchor cables for offshore drilling rigs and reinforcement fibers for automobile tires. Kevlar is also woven into a fabric that is so tough that it can be used for bulletproof vests, jackets, and raincoats.

B. Polyesters

The first **polyester**, developed in the 1940s, involved the polymerization of benzene 1,4-dicarboxylic acid (terephthalic acid) with 1,2-ethanediol (ethylene glycol) to give poly(ethylene terephthalate), abbreviated PET or PETE. Virtually all PET is now made from the dimethyl ester of terephthalic acid by the following transesterification reaction (Section 14.4C):



Dimethyl terephthalate — 1,2-Ethanediol (Ethylene glycol) — Poly(ethylene terephthalate) (Dacron®, Mylar®)

Polyester A polymer in which each monomer unit is joined to the next by an ester bond as, for example, poly(ethylene terephthalate).

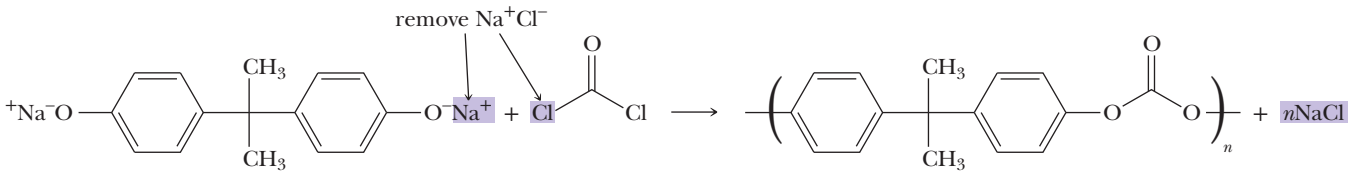
The crude polyester can be melted, extruded, and then cold drawn to form the textile fiber Dacron® polyester, the outstanding features of which are its stiffness (about four times that of nylon 66), very high strength, and remarkable resistance to creasing and wrinkling. Because the early Dacron® polyester fibers were harsh to the touch, due to their stiffness, they were usually blended with cotton or wool to make acceptable textile fibers. Newly

developed fabrication techniques now produce less harsh Dacron® polyester textile fibers. PET is also fabricated into Mylar® films and recyclable plastic beverage containers.

C. Polycarbonates

Polycarbonates, the most familiar of which is Lexan®, are a class of commercially important engineering polyesters. Lexan® forms by the reaction between the disodium salt of bisphenol A (Problem 9.33) and phosgene:

Polycarbonate A polyester in which the carboxyl groups are derived from carbonic acid.



Disodium salt of bisphenol A — Phosgene — Lexan® (a polycarbonate)

Note that phosgene is the diacid chloride (Section 14.1A) of carbonic acid; hydrolysis of phosgene gives H_2CO_3 and 2HCl.

Lexan® is a tough, transparent polymer with high impact and tensile strengths that retains its properties over a wide temperature range. It is used in sporting equipment (for helmets and face masks), in the production of light, impact-resistant housings for household appliances, and in the manufacture of safety glass and unbreakable windows.

Charles D. Winters

A polycarbonate hockey mask.

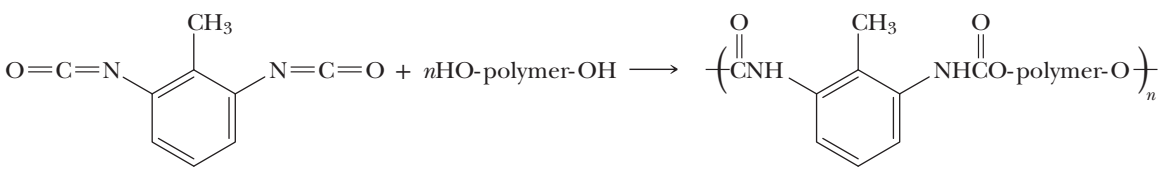
D. Polyurethanes

A urethane, or carbamate, is an ester of carbamic acid, H_2NCOOH. Carbamates are most commonly prepared by treating an isocyanate with an alcohol. In this reaction, the H and OR′ of the alcohol add to the C═N bond in a reaction comparable to the addition of an alcohol to a C═O bond:

An isocyanate — A carbamate

Polyurethanes consist of flexible polyester or polyether units (blocks) alternating with rigid urethane units (blocks) derived from a diisocyanate, commonly a mixture of 2,4- and 2,6-toluene diisocyanate:

Polyurethane A polymer containing the —NHCOO— group as a repeating unit.



2,6-Toluene diisocyanate — Low-molecular-weight polyester or polyether with OH groups at each end of the chain — A polyurethane

The more flexible blocks are derived from low-molecular-weight (1,000 to 4,000) polyesters or polyethers with —OH groups at each end of their chains. Polyurethane fibers are fairly soft and elastic and have found use as spandex and Lycra®, the "stretch" fabrics used in bathing suits, leotards, and undergarments.

Polyurethane foams for upholstery and insulating materials are made by adding small amounts of water during polymerization. Water reacts with isocyanate groups to form a

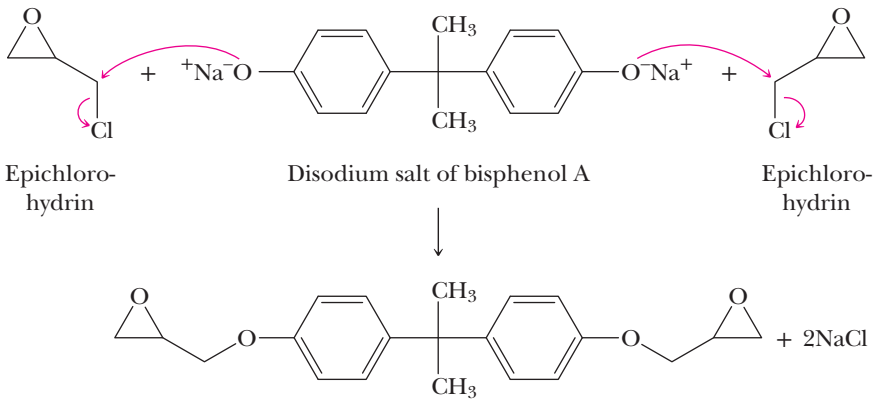
carbamic acid that undergoes spontaneous decarboxylation to produce gaseous carbon dioxide, which then acts as the foaming agent:

An isocyanate — A carbamic acid (unstable)

E. Epoxy Resins

Epoxy resin A material prepared by a polymerization in which one monomer contains at least two epoxy groups.

Epoxy resins are materials prepared by a polymerization in which one monomer contains at least two epoxy groups. Within this range, a large number of polymeric materials are possible, and epoxy resins are produced in forms ranging from low-viscosity liquids to high-melting solids. The most widely used epoxide monomer is the diepoxide prepared by treating one mole of the disodium salt of bisphenol A (Problem 9.33) with two moles of epichlorohydrin:

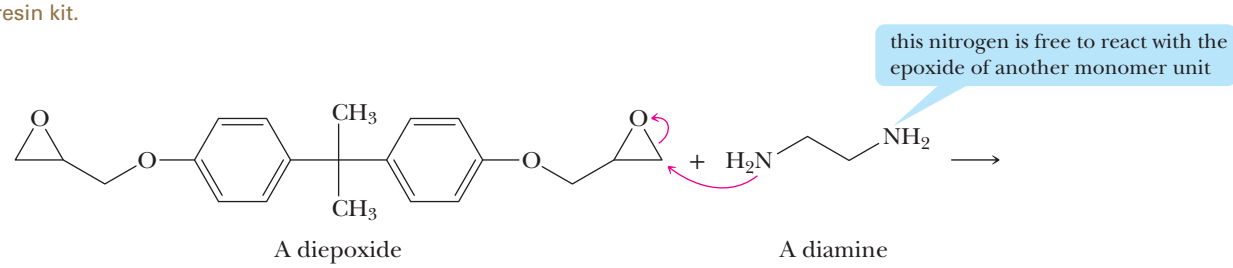


A diepoxide

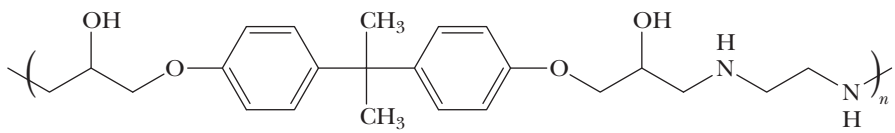
Charles D. Winters

An epoxy resin kit.

To prepare the following epoxy resin, the diepoxide monomer is treated with 1,2-ethanediamine (ethylene diamine):



A diepoxide — A diamine



An epoxy resin

Ethylene diamine is usually labeled the catalyst in the two-component formulations that you buy in hardware or craft stores; it is also the component with the acrid smell. The preceding reaction corresponds to nucleophilic opening of the highly strained three-membered epoxide ring (Section 8.4C).

Epoxy resins are widely used as adhesives and insulating surface coatings. They have good electrical insulating properties, which lead to their use in encapsulating electrical components ranging from integrated circuit boards to switch coils and insulators for power transmission systems. Epoxy resins are also used as composites with other materials, such as glass fiber, paper, metal foils, and other synthetic fibers, to create structural components for jet aircraft, rocket motor casings, and so on.

EXAMPLE 16.2

By what type of mechanism does the reaction between the disodium salt of bisphenol A and epichlorohydrin take place?

STRATEGY

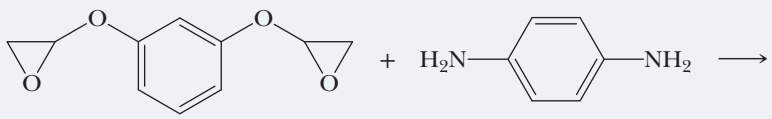
Examine the mechanism on the previous page and you will see by the curved arrows that an oxygen anion of bisphenol A displaces a chlorine atom from the primary carbon of epichlorohydrin. The phenoxide ion of bisphenol A is a good nucleophile, and chlorine on the primary carbon of epichlorohydrin is the leaving group.

SOLUTION

The mechanism is an S_N2 mechanism.

PROBLEM 16.2

Write the repeating unit of the epoxy resin formed from the following reaction:



A diepoxide + A diamine

16.5 What Are Chain-Growth Polymers?

From the perspective of the chemical industry, the single most important reaction of alkenes is **chain-growth polymerization**, a type of polymerization in which monomer units are joined together without the loss of atoms. An example is the formation of polyethylene from ethylene:

Chain-growth polymerization A polymerization that involves sequential addition reactions, either to unsaturated monomers or to monomers possessing other reactive functional groups.

$$n\mathrm{CH_2{=}CH_2} \xrightarrow{\text{catalyst}} \text{—}(\mathrm{CH_2CH_2})_n\text{—}$$

Ethylene → Polyethylene

The mechanisms of chain-growth polymerization differ greatly from the mechanism of step-growth polymerizations. In the latter, all monomers plus the polymer end groups possess equally reactive functional groups, allowing for all possible combinations of reactions to occur, including monomer with monomer, dimer with dimer, monomer with tetramer, and so forth. In contrast, chain-growth polymerizations involve end groups possessing reactive intermediates that react only with a monomer. The reactive intermediates used in chain-growth polymerizations include radicals, carbanions, carbocations, and organometallic complexes.

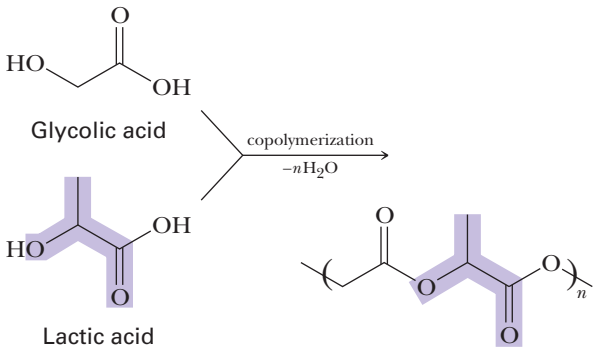
Chemical Connections 16A

STITCHES THAT DISSOLVE

As the technological capabilities of medicine have grown, the demand for synthetic materials that can be used inside the body has increased as well. Polymers have many of the characteristics of an ideal biomaterial: They are lightweight and strong, are inert or biodegradable (depending on their chemical structure), and have physical properties (softness, rigidity, elasticity) that are easily tailored to match those of natural tissues. Carbon–carbon backbone polymers are resistant to degradation and are used widely in permanent organ and tissue replacements.

Even though most medical uses of polymeric materials require biostability, applications have been developed that use the biodegradable nature of some macromolecules. An example is the use of

glycolic acid/lactic acid copolymers as absorbable sutures:



A copolymer of poly(glycolic acid)–poly(lactic acid)

Traditional suture materials such as catgut must be removed by a health-care specialist after they have served their purpose. Stitches of these hydroxyester polymers, however, are hydrolyzed slowly over a period of approximately two weeks, and by the time the torn tissues have fully healed, the stitches are fully degraded and the sutures need not be removed. Glycolic and lactic acids formed during hydrolysis of the stitches are metabolized and excreted by existing biochemical pathways.

Question

Propose a mechanism for the hydrolysis of one repeating unit of the copolymer of poly(glycolic acid)-poly(lactic acid).

The number of monomers that undergo chain-growth polymerization is large and includes such compounds as alkenes, alkynes, allenes, isocyanates, and cyclic compounds such as lactones, lactams, ethers, and epoxides. We concentrate on the chain-growth polymerizations of ethylene and substituted ethylenes and show how these compounds can be polymerized by radical and organometallic-mediated mechanisms.

Table 16.1 lists several important polymers derived from ethylene and substituted ethylenes, along with their common names and most important uses.

A. Radical Chain-Growth Polymerization

Radical Any molecule that contains one or more unpaired electrons.

The first commercial polymerizations of ethylene were initiated by radicals formed by thermal decomposition of organic peroxides, such as benzoyl peroxide. A **radical** is any molecule that contains one or more unpaired electrons. Radicals can be formed by the cleavage of a bond in such a way that each atom or fragment participating in the bond retains one

TABLE 16.1 Polymers Derived from Ethylene and Substituted Ethylenes

Monomer Formula	Common Name	Polymer Name(s) and Common Uses
$CH_2{=}CH_2$	Ethylene	Polyethylene, Polythene; break-resistant containers and packaging materials
$CH_2{=}CHCH_3$	Propylene	Polypropylene, Herculon™; textile and carpet fibers
$CH_2{=}CHCl$	Vinyl chloride	Poly(vinyl chloride), PVC; construction tubing
$CH_2{=}CCl_2$	1,1-Dichloroethylene	Poly(1,1-dichloroethylene); Saran Wrap® is a copolymer with vinyl chloride
$CH_2{=}CHCN$	Acrylonitrile	Polyacrylonitrile, Orlon®; acrylics and acrylates
$CF_2{=}CF_2$	Tetrafluoroethylene	Polytetrafluoroethylene, PTFE; Teflon®, nonstick coatings
$CH_2{=}CHC_6H_5$	Styrene	Polystyrene, Styrofoam™; insulating materials
$CH_2{=}CHCOOCH_2CH_3$	Ethyl acrylate	Poly(ethyl acrylate); latex paints
$CH_2{=}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}COOCH_3$	Methyl methacrylate	Poly(methyl methacrylate), Lucite®, Plexiglas®; glass substitutes

Chemical Connections 16B

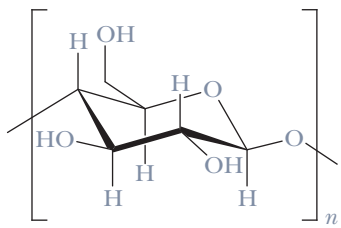
PAPER OR PLASTIC?

Any audiophile will tell you that the quality of any sound system is highly dependent on its speakers. Speakers create sound by moving a diaphragm in and out to displace air. Most diaphragms are in the shape of a cone, traditionally made of paper. Paper cones are inexpensive, lightweight, rigid, and nonresonant. One disadvantage is their susceptibility to damage by water and humidity. Over time and with exposure, paper cones become weakened, losing their fidelity of sound. Many of the speakers that are available today are made of polypropylene, which is also inexpensive, lightweight, rigid, and nonresonant. Furthermore, not only are polypropylene cones immune to water and humidity, but also their performance is less influenced by heat or cold. Moreover, their added strength makes them less prone to splitting than paper. They last longer and can be displaced more frequently and for longer distances, creating deeper bass notes and higher high notes.

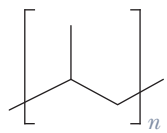
© perets/iStockphoto

Question

Paper speaker cones consist of mostly cellulose, a polymer of the monomer unit known as D-glucose (Chapter 17). Propose why one type of polymer is susceptible to humidity while the other type, polypropylene, is resistant to humidity.



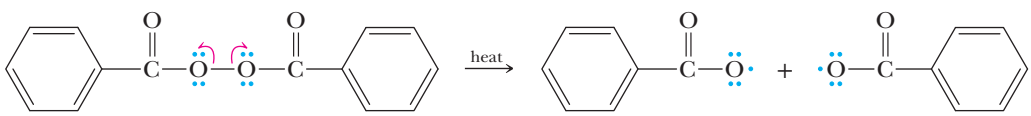
Cellulose



Polypropylene

electron. In the following equation, **fishhook arrows** are used to show the change in position of single electrons:

Fishhook arrow A single-barbed, curved arrow used to show the change in position of a single electron.



Benzoyl peroxide — Benzoyloxy radicals

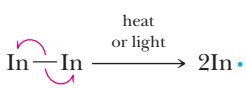
Radical polymerization of ethylene and substituted ethylenes involves three steps: (1) chain initiation, (2) chain propagation, and (3) chain termination. We show these steps here and then discuss each separately in turn.

Mechanism

Radical Polymerization of Ethylene

STEP 1: *Chain initiation*—formation of radicals from nonradical compounds:

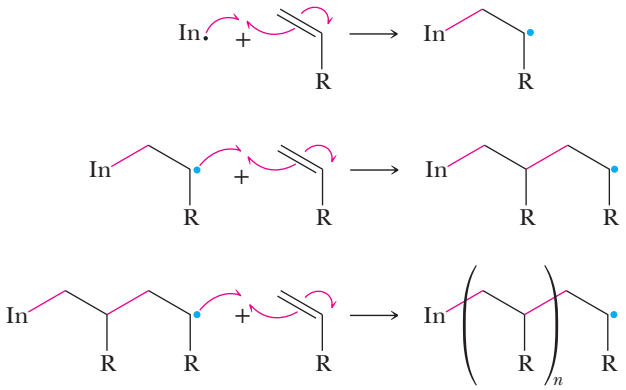
Chain initiation In radical polymerization, the formation of radicals from molecules containing only paired electrons.



In this equation, In-In represents an initiator that, when heated or irradiated with radiation of a suitable wavelength, cleaves to give two radicals (In·).

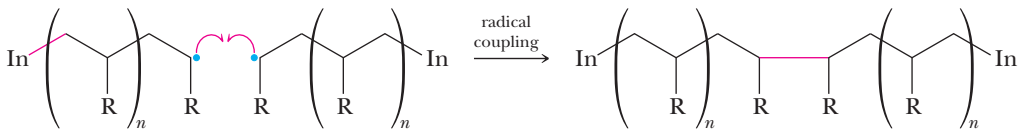
Chain propagation In radical polymerization, a reaction of a radical and a molecule to give a new radical.

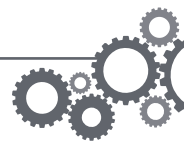
STEP 2: *Chain propagation*—reaction of a radical and a molecule to form a new radical:



STEP 3: *Chain termination*—destruction of radicals:

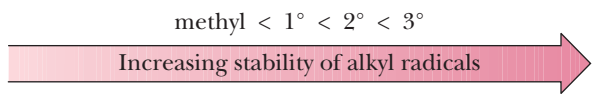
Chain termination In radical polymerization, a reaction in which two radicals combine to form a covalent bond.





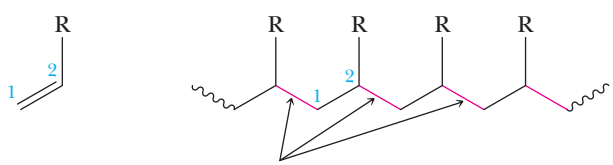
The characteristic feature of a chain-initiation step is the formation of radicals from a molecule with only paired electrons. In the case of peroxide-initiated polymerizations of alkenes, chain initiation is by (1) heat cleavage of the O—O bond of a peroxide to give two alkoxy radicals and (2) reaction of an alkoxy radical with a molecule of alkene to give an alkyl radical. In the general mechanism shown, the initiating catalyst is given the symbol In-In and its radical is given the symbol In·.

The structure and geometry of carbon radicals are similar to those of alkyl carbocations. They are planar or nearly so, with bond angles of approximately 120° about the carbon with the unpaired electron. The relative stabilities of alkyl radicals are similar to those of alkyl carbocations because they both possess electron-deficient carbons.



The characteristic feature of a chain-propagation step is the reaction of a radical and a molecule to give a new radical. Propagation steps repeat over and over (propagate), with the radical formed in one step reacting with a monomer to produce a new radical, and so on. The number of times a cycle of chain-propagation steps repeats is called the **chain length** and is given the symbol ***n***. In the polymerization of ethylene, chain-lengthening reactions occur at a very high rate, often as fast as thousands of additions per second, depending on the experimental conditions.

Radical polymerizations of substituted ethylenes almost always give the more stable (more substituted) radical. Because additions are biased in this fashion, the polymerizations of substituted ethylene monomers tend to yield polymers with monomer units joined by the head (carbon 1) of one unit to the tail (carbon 2) of the next unit:



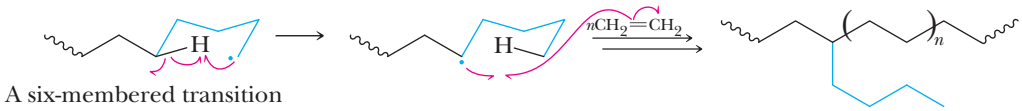
Substituted ethylene monomer

Head-to-tail linkages

In principle, chain-propagation steps can continue until all starting materials are consumed. In practice, they continue only until two radicals react with each other to terminate the process. The characteristic feature of a chain-termination step is the destruction of radicals. In the mechanism shown for radical polymerization of the substituted ethylene, chain termination occurs by the coupling of two radicals to form a new carbon–carbon single bond.

The first commercial process for ethylene polymerization used peroxide catalysts at temperatures of 500 °C and pressures of 1,000 atm and produced a soft, tough polymer known as **low-density polyethylene (LDPE)** with a density of between 0.91 and 0.94 g/cm^3 and a melt transition temperature (T_m) of about 115 °C. Because LDPE's melting point is only slightly above 100 °C, it cannot be used for products that will be exposed to boiling water. At the molecular level, chains of LDPE are highly branched.

The branching on chains of low-density polyethylene results from a "back-biting" reaction in which the radical end group abstracts a hydrogen from the fourth carbon back (the fifth carbon in the chain). Abstraction of this hydrogen is particularly facile because the transition state associated with the process can adopt a conformation like that of a chair cyclohexane. In addition, the less stable 1° radical is converted to a more stable 2° radical. This side reaction is called a **chain-transfer reaction**, because the activity of the end group is "transferred" from one chain to another. Continued polymerization of monomer from this new radical center leads to a branch four carbons long:



A six-membered transition state leading to 1,5-hydrogen abstraction

Chain-transfer reaction
In radical polymerization, the transfer of reactivity of an end group from one chain to another during a polymerization.

Approximately 65% of all LDPE is used for the manufacture of films by a blow-molding technique illustrated in Figure 16.5. LDPE film is inexpensive, which makes it ideal for packaging such consumer items as baked goods, vegetables, and other produce and for trash bags.

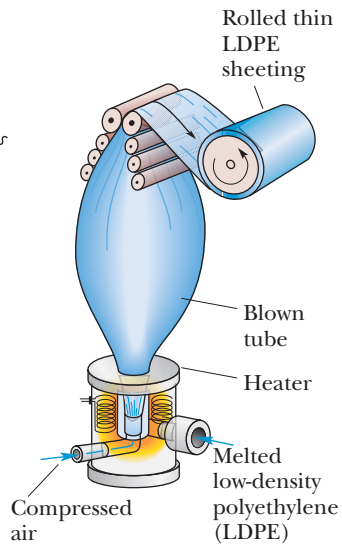


FIGURE 16.5 Fabrication of an LDPE film. A tube of melted LDPE along with a jet of compressed air is forced through an opening and blown into a giant, thin-walled bubble. The film is then cooled and taken up onto a roller. This double-walled film can be slit down the side to give LDPE film, or it can be sealed at points along its length to make LDPE bags.

B. Ziegler–Natta Chain-Growth Polymerization

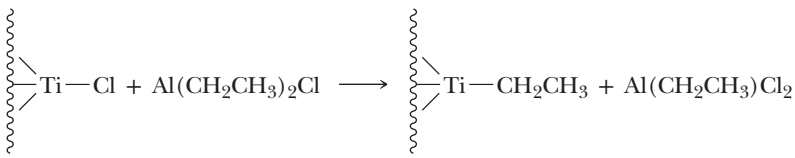
In the 1950s, Karl Ziegler of Germany and Giulio Natta of Italy developed an alternative method for the polymerization of alkenes, work for which they shared the Nobel Prize for chemistry in 1963. The early Ziegler–Natta catalysts were highly active, heterogeneous materials composed of an $MgCl_2$ support, a Group 4B transition metal halide such as $TiCl_4$, and an alkylaluminum compound—for example, diethylaluminum chloride, $Al(CH_2CH_3)_2Cl$. These catalysts bring about the polymerization of ethylene and propylene at 1–4 atm and at temperatures as low as 60 °C.

The catalyst in a Ziegler–Natta polymerization is an alkyltitanium compound formed by reaction between $Al(CH_2CH_3)_2Cl$ and the titanium halide on the surface of a $MgCl_2$/$TiCl_4$ particle. Once formed, this alkyltitanium species repeatedly inserts ethylene units into the titanium–carbon bond to yield polyethylene.

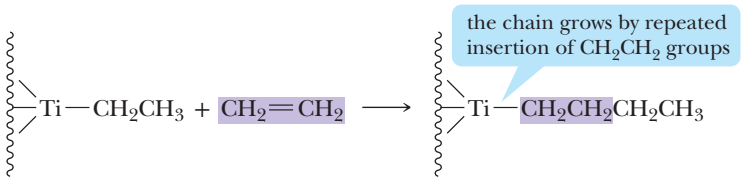
Mechanism

Ziegler–Natta Catalysis of Ethylene Polymerization

STEP 1: *Formation of a titanium–ethyl bond:*



STEP 2: *Insertion of ethylene into the titanium–carbon bond:*



Polyethylene films are produced by extruding the molten plastic through a ring-like gap and inflating the film into a balloon.

Over 60 billion pounds of polyethylene are produced worldwide every year with Ziegler–Natta catalysts. Polyethylene from Ziegler–Natta systems, termed **high-density polyethylene (HDPE)**, has a higher density (0.96 g/cm^3) and melt transition temperature (133 °C) than low-density polyethylene (0.91 g/cm^3 and 115 °C, respectively), is 3 to 10 times stronger, and is opaque rather than transparent. The added strength and opacity are due to a much lower degree of chain branching and a resulting higher degree of crystallinity of HDPE compared with LDPE. Approximately 45% of all HDPE used in the United States is blow molded (Figure 16.6).

Even greater improvements in properties of HDPE can be realized through special processing techniques. In the melt state, HDPE chains have random coiled conformations similar to those of cooked spaghetti. Engineers have developed extrusion techniques that force the individual polymer chains of HDPE to uncoil into linear conformations. These linear chains then align with one another to form highly crystalline materials. HDPE processed in this fashion is stiffer than steel and has approximately four times its tensile strength! Because the density of polyethylene (≈ 1.0 g/cm^3) is considerably less than that of steel (8.0 g/cm^3), these comparisons of strength and stiffness are even more favorable if they are made on a weight basis.

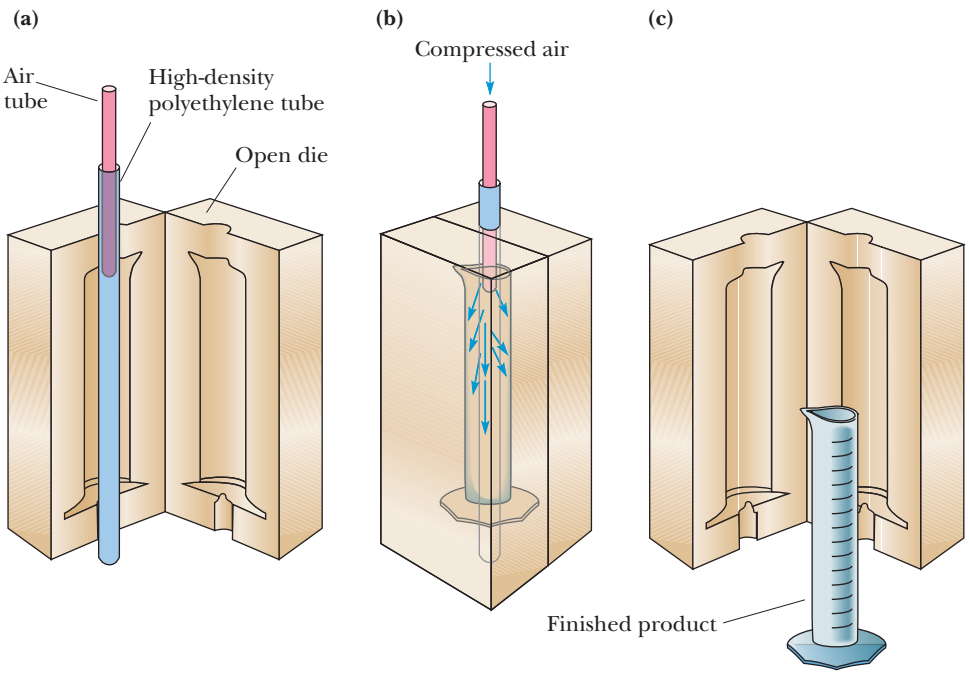


FIGURE 16.6 Blow molding of an HDPE container. (a) A short length of HDPE tubing is placed in an open die, and the die is closed, sealing the bottom of the tube. (b) Compressed air is forced into the hot polyethylene–die assembly, and the tubing is literally blown up to take the shape of the mold. (c) After cooling, the die is opened, and there is the container!

16.6 What Plastics Are Currently Recycled in Large Quantities?

Our society is incredibly dependent on polymers in the form of plastics. Durable and lightweight, plastics are probably the most versatile synthetic materials in existence; in fact, their current production in the United States exceeds that of steel. Plastics have come under criticism, however, for their role in the current trash crisis. They make up 21% of the volume and 8% of the weight of solid waste, most of which is derived from disposable packaging and wrapping. Of the 1.5×10^8 kg of thermoplastic materials produced in the United States per year, less than 2% is recycled.

If the durability and chemical inertness of most plastics make them ideally suited for reuse, why aren't more plastics being recycled? The answer to this question has more to do with economics and consumer habits than with technological obstacles. Because curbside pickup and centralized drop-off stations for recyclables are just now becoming common, the amount of used material available for reprocessing has traditionally been small. This limitation, combined with the need for an additional sorting and separation step, rendered the use of recycled plastics in manufacturing expensive compared with virgin materials. The increase in environmental awareness over the last decade, however, has resulted in a greater demand for recycled products. As manufacturers adapt to satisfy this new market, the recycling of plastics will eventually catch up with that of other materials, such as glass and aluminum.

Six types of plastics are commonly used for packaging applications. In 1988, manufacturers adopted recycling code numbers developed by the Society of the Plastics Industry (Table 16.2). Because the plastics recycling industry still is not fully developed, only PET and HDPE are currently being recycled in large quantities. LDPE, which accounts for about 40% of plastic trash, has been slow in finding acceptance with recyclers. Facilities for the reprocessing of poly(vinyl chloride) (PVC), polypropylene (PP), and polystyrene (PS) exist but are rare.

The process for the recycling of most plastics is simple, with separation of the desired plastics from other contaminants the most labor-intensive step. For example, PET

Charles D. Winters

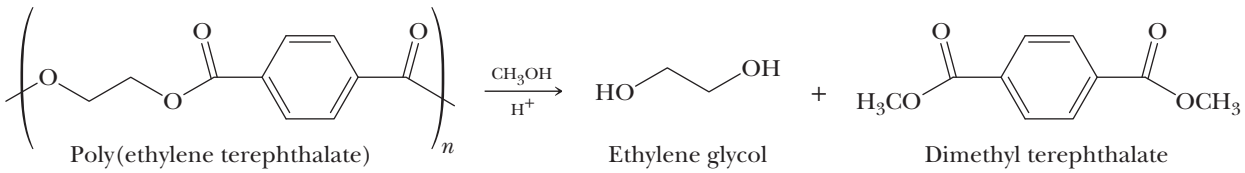
Some common products packaged in high-density polyethylene containers.

TABLE 16.2 Recycling Codes for Plastics

Recycling Code	Polymer	Common Uses	Uses of Recycled Polymer
1 PET	Poly(ethylene terephthalate)	Soft-drink bottles, household chemical bottles, films, textile fibers	Soft-drink bottles, household chemical bottles, films, textile fibers
2 HDPE	High-density polyethylene	Milk and water jugs, grocery bags, bottles	Bottles, molded containers
3 V	Poly(vinyl chloride), PVC	Shampoo bottles, pipes, shower curtains, vinyl siding, wire insulation, floor tiles, credit cards	Plastic floor mats
4 LDPE	Low-density polyethylene	Shrink wrap, trash and grocery bags, sandwich bags, squeeze bottles	Trash bags and grocery bags
5 PP	Polypropylene	Plastic lids, clothing fibers, bottle caps, toys, diaper linings	Mixed-plastic components
6 PS	Polystyrene	Styrofoam™ cups, egg cartons, disposable utensils, packaging materials, appliances	Molded items such as cafeteria trays, rulers, Frisbees™, trash cans, videocassettes
7	All other plastics and mixed plastics	Various	Plastic lumber, playground equipment, road reflectors

soft-drink bottles usually have a paper label and adhesive that must be removed before the PET can be reused. The recycling process begins with hand or machine sorting, after which the bottles are shredded into small chips. An air cyclone then removes paper and other lightweight materials. Any remaining labels and adhesives are eliminated with a detergent wash, and the PET chips are then dried. PET produced by this method is 99.9% free of contaminants and sells for about half the price of the virgin material. Unfortunately, plastics with similar densities cannot be separated with this technology, nor can plastics composed of several polymers be broken down into pure components. However, recycled mixed plastics can be molded into plastic lumber that is strong, durable, and resistant to graffiti.

An alternative to the foregoing process, which uses only physical methods of purification, is chemical recycling. Large amounts of PET film scrap are salvaged by a transesterification reaction. The scrap is treated with methanol in the presence of an acid catalyst to give ethylene glycol and dimethyl terephthalate, monomers that are purified by distillation or recrystallization and used as feedstocks for the production of more PET film:



Poly(ethylene terephthalate) (PET) | Ethylene glycol | Dimethyl terephthalate

SUMMARY OF KEY QUESTIONS

16.1 What Is the Architecture of Polymers?

- **Polymerization** is the process of joining together many small **monomers** into large, high-molecular-weight **polymers**.
- **Polymers** are long-chain molecules synthesized by linking monomers through chemical reactions. The molecular weight of polymers is generally high compared with those of common organic compounds, and typically range from 10,000 g/mol to more than 1,000,000 g/mol.
- **Thermoplastics** are polymers that can be molded when hot and that retain their shape when cooled.
- **Thermosetting plastics** can be molded when they are first prepared, but once cooled, they harden irreversibly and cannot be remelted.

16.2 How Do We Name and Show the Structure of a Polymer?

- The **repeat unit** of a polymer is the smallest unit that contains all of the structural features of the polymer.
- To show the structure of a polymer, enclose the repeat unit in parentheses and place a subscript *n* outside the parentheses to show that this structural unit repeats *n* times in a polymer chain.
- An entire polymer chain can be reproduced by repeating the enclosed structural unit in both directions.
- The most common method of naming a polymer is to add the prefix **poly-** to the name of the monomer from which the polymer is synthesized. If the name of the monomer is two or more words, enclose its name in parentheses.

16.3 What Is Polymer Morphology? Crystalline versus Amorphous Materials

- The properties of polymeric materials depend on the structure of the repeat unit, as well as on the **chain architecture** and **morphology** of the material.
- Polymers, like small organic molecules, tend to crystallize upon precipitation or as they are cooled from a melt.
- Acting to inhibit crystallization are the facts that polymer molecules are very large, which inhibits their diffusion, and that their structures are sometimes complicated and irregular.
- Polymers in the solid state tend to be composed of both ordered **crystalline domains** (crystallites) and disordered **amorphous domains**.
- The temperature at which a polymer undergoes the transition from a hard glass to a rubbery state corresponds to the **glass transition temperature (T_g)**.
- As the degree of crystallinity of a polymer increases, the polymer becomes more opaque because of the scattering

of light by its crystalline domains. With an increase in crystallinity comes an increase in strength and stiffness.

- Amorphous polymers have little or no long-range order. Because they lack crystalline domains that scatter light, amorphous polymers are transparent. In addition, they tend to be highly flexible and have low mechanical strength.

16.4 What Is Step-Growth Polymerization?

- **Step-growth polymerizations** involve the stepwise reaction of difunctional monomers.
- The two most common types of step-growth polymerizations involve (1) reaction between A-M-A and B-M-B monomers to give – (A-M-A-B-M-B)*n*- polymers, where A and B are reactive functional groups, and (2) self-condensations of A-M-B monomers to give –(A-M-B)*n*-polymers.
- Important commercial polymers synthesized through step-growth processes include polyamides, polyesters, polycarbonates, polyurethanes, and epoxy resins.

16.5 What Are Chain-Growth Polymers?

- **Chain-growth polymerization** proceeds by the sequential addition of monomer units to an active chain end-group.
- **Radical chain-growth polymerization** consists of three stages: chain initiation, chain propagation, and chain termination.
- **Alkyl radicals** are planar or almost so with bond angles of approximately 120° about the carbon with the unpaired electron.
- In **chain initiation**, radicals are formed from nonradical molecules.
- In **chain propagation**, a radical and a monomer react to give a new radical.
- **Chain length** is the number of times a cycle of chain propagation steps repeats.
- In **chain termination**, radicals are destroyed.
- **Ziegler–Natta chain-growth polymerization** involves the formation of an alkyl-transition metal compound and then the repeated insertion of alkene monomers into the transition metal-to-carbon bond to yield a saturated polymer chain.

16.6 What Plastics Are Commonly Recycled in Large Quantities?

- The six types of plastics commonly used for packaging applications have been assigned recycling codes with values 1 through 6.
- Currently, only (1) poly(ethylene terephthalate), PET, and (2) high-density polyethylene (HDPE) are recycled in large quantities.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. Radicals can undergo chain-growth polymerization. (16.5)
2. A thermosetting plastic cannot be remelted. (16.1)
3. Chain-transfer reactions can lead to branching in polymers. (16.5)
4. Polymers that have low glass transition temperatures can behave as elastomers. (16.3)
5. A highly crystalline polymer will have a glass transition temperature. (16.3)
6. Polymers can be named from the monomeric units from which they are derived. (16.2)
7. Only compounds that have two or more functional groups can undergo step-growth polymerization. (16.4)
8. The propagation step of a radical polymerization mechanism involves the reaction of a radical with another radical. (16.5)
9. A radical is a molecule with an unpaired electron and a positive charge. (16.5)
10. The term *plastics* can be used to refer to all polymers. (16.1)
11. The mechanism of a radical polymerization reaction involves three distinct steps. (16.5)
12. Hydrogen bonding will usually weaken the fibers of a polymer. (16.4)
13. A secondary radical is more stable than a tertiary radical. (16.5)
14. A thermoplastic can be molded multiple times through heating and cooling. (16.1)
15. Ziegler–Natta polymerization uses a titanium catalyst. (16.5)

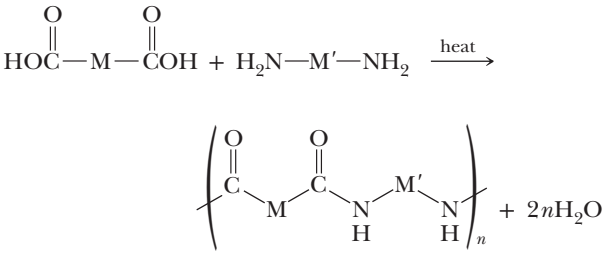
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) T (3) T (4) T (5) F (6) T (7) T (8) F (9) F (10) F (11) T (12) F (13) F (14) T (15) T

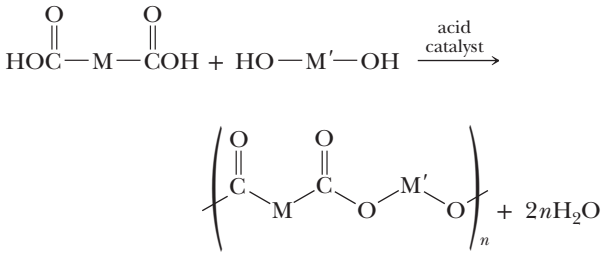
KEY REACTIONS

1. Step-growth polymerization of a dicarboxylic acid and a diamine gives a polyamide (Section 16.4A)

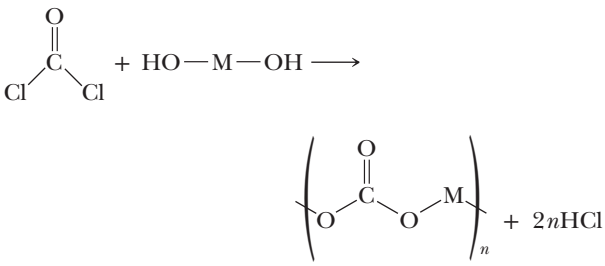
In this equation, M and M′ indicate the remainder of each monomer unit:



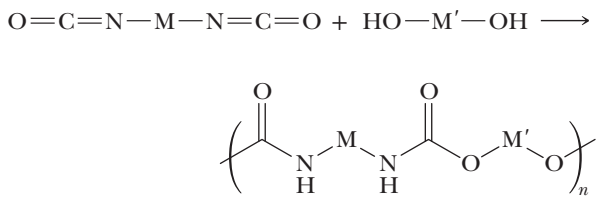
2. Step-growth polymerization of a dicarboxylic acid and a diol gives a polyester (Section 16.4B)



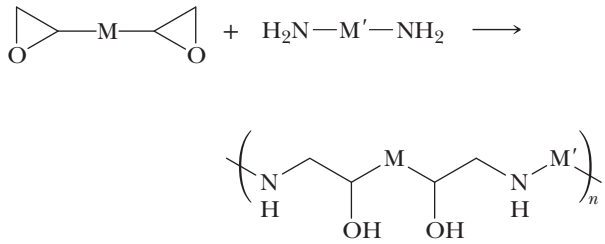
3. Step-growth polymerization of phosgene and a diol gives a polycarbonate (Section 16.4C)



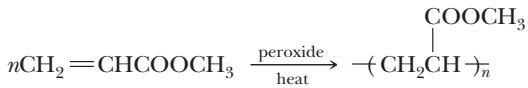
4. Step-growth polymerization of a diisocyanate and a diol gives a polyurethane (Section 16.4D)



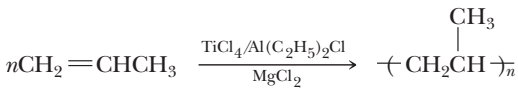
5. Step-growth polymerization of a diepoxide and a diamine gives an epoxy resin (Section 16.4E)



6. Radical chain-growth polymerization of ethylene and substituted ethylenes (Section 16.5A)



7. Ziegler–Natta chain-growth polymerization of ethylene and substituted ethylenes (Section 16.5B)



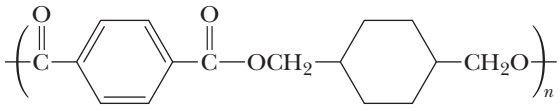
PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 16.4 Step-Growth Polymers

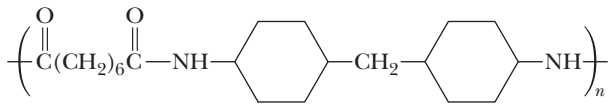
***16.3** Identify the monomers required for the synthesis of each step-growth polymer:

(a)



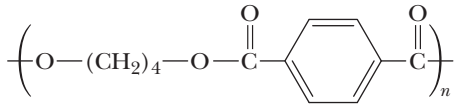
Kodel™
(a polyester)

(b)

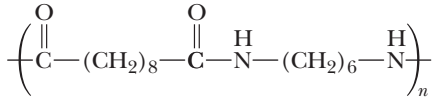


Quiana™
(a polyamide)

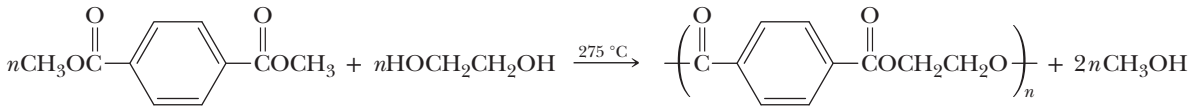
(c)



(d)



***16.4** Poly(ethylene terephthalate) (PET) can be prepared by the following reaction:

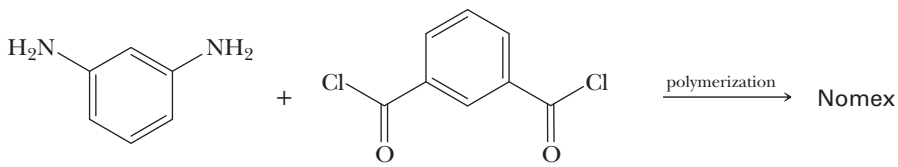


Dimethyl terephthalate | Ethylene glycol | Poly(ethylene terephthalate) | Methanol

Propose a mechanism for the step-growth reaction in this polymerization.

***16.5** Currently, about 30% of PET soft-drink bottles are being recycled. In one recycling process, scrap PET is heated with methanol in the presence of an acid catalyst. The methanol reacts with the polymer, liberating ethylene glycol and dimethyl terephthalate. These monomers are then used as feedstock for the production of new PET products. Write an equation for the reaction of PET with methanol to give ethylene glycol and dimethyl terephthalate.

***16.6** Nomex® is an aromatic polyamide (aramid) prepared from the polymerization of 1,3-benzenediamine and the acid chloride of 1,3-benzenedicarboxylic acid:



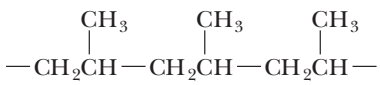
1,3-Benzenediamine | 1,3-Benzene-dicarbonyl chloride

The physical properties of the polymer make it suitable for high-strength, high-temperature applications such as parachute cords and jet aircraft tires. Draw a structural formula for the repeating unit of Nomex.

16.7 Nylon 6,10 [Problem 16.3(d)] can be prepared by reacting a diamine and a diacid chloride. Draw the structural formula of each reactant.

SECTION 16.5 Chain-Growth Polymerization

16.8 Following is the structural formula of a section of polypropylene derived from three units of propylene monomer:



Polypropylene

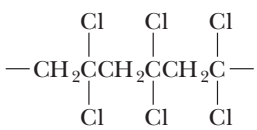
Draw a structural formula for a comparable section of

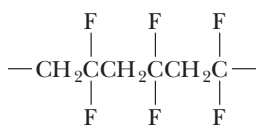
(a) Poly(vinyl chloride)

(b) Polytetrafluoroethylene (PTFE)

(c) Poly(methyl methacrylate)

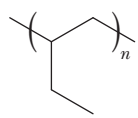
16.9 Following are structural formulas for sections of two polymers: **(See Example 16.1)**

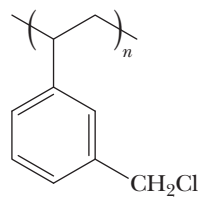
(a) 

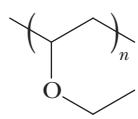
(b) 

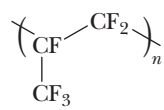
From what alkene monomer is each polymer derived?

16.10 Draw the structure of the alkene monomer used to make each chain-growth polymer: **(See Example 16.1)**

(a) 

(c) 

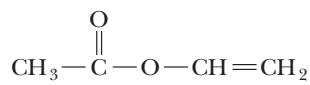
(b) 

(d) 

16.11 LDPE has a higher degree of chain branching than HDPE. Explain the relationship between chain branching and density.

16.12 Compare the densities of LDPE and HDPE with the densities of the liquid alkanes listed in Table 3.4. How might you account for the differences between them?

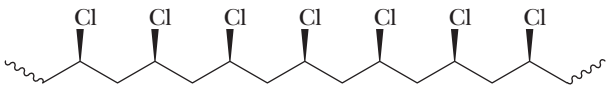
16.13 The polymerization of vinyl acetate gives poly(vinyl acetate). Hydrolysis of this polymer in aqueous sodium hydroxide gives poly(vinyl alcohol). Draw the repeat units of both poly(vinyl acetate) and poly(vinyl alcohol):

Vinyl acetate 

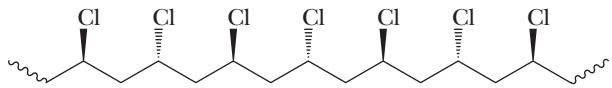
16.14 As seen in the previous problem, poly(vinyl alcohol) is made by the polymerization of vinyl acetate, followed by hydrolysis in aqueous sodium hydroxide. Why is poly(vinyl alcohol) not made instead by the polymerization of vinyl alcohol, $CH_2{=}CHOH$?

16.15 As you know, the shape of a polymer chain affects its properties. Consider the following three polymers:

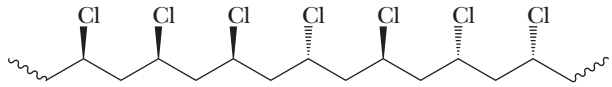
A



B



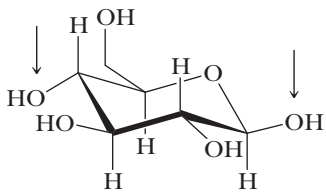
C



Which do you expect to be the most rigid? Which do you expect to be the most transparent? (Assume the same molecular weights.)

LOOKING AHEAD

***16.16** Cellulose, the principal component of cotton, is a polymer of D-glucose in which the monomer unit repeats at the indicated atoms:

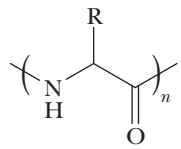


D-Glucose

Draw a three-unit section of cellulose.

16.17 Is a repeating unit a requirement for a compound to be called a polymer?

***16.18** Proteins are polymers of naturally occurring monomers called amino acids:



a protein

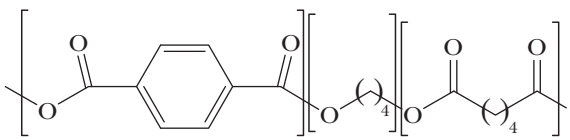
Amino acids differ in the types of R groups available in nature. Explain how the following properties of a protein might be affected upon changing the R groups from $-CH_2CH(CH_3)_2$ to $-CH_2OH$:

(a) solubility in water
(b) melting point
(c) crystallinity
(d) elasticity

GROUP LEARNING ACTIVITIES

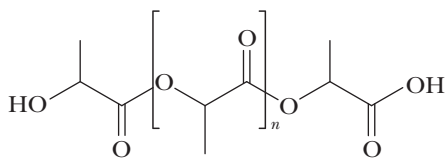
***16.19** Only certain kinds of polymers are readily biodegradable; that is, only certain types have chemical bonds that are easily broken in the process of composting. Chief among these polymers are those that contain ester bonds because ester bonds are readily broken by esterases, microbial enzymes that catalyze the hydrolysis of esters. For this reason, all presently available biodegradable polymers are polyesters. Following are structural formulas for three such biodegradable polyesters. As a group, draw structural formulas and write names for the monomer units present in each. Provide a mechanism for the acid-catalyzed hydrolysis of all hydrolyzable bonds in Ecoflex.

(a)



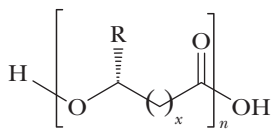
Ecoflex (BASF)

(b)

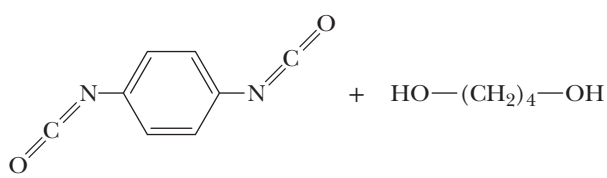


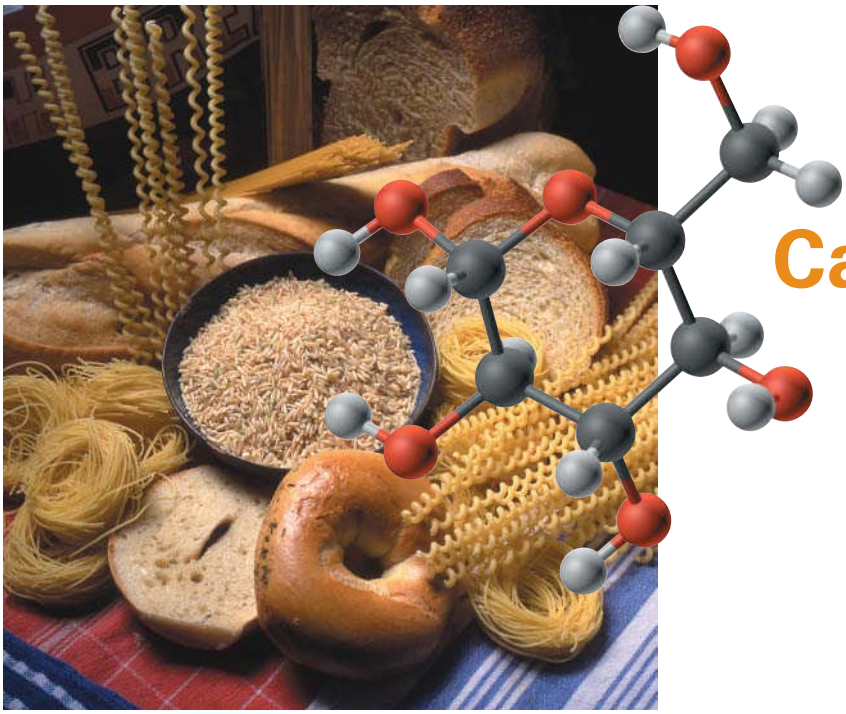
Polylactic Acid (PLA)

(c)



16.20 The two monomers shown form a polyurethane (Section 16.4D). Propose a structure for the polymer and a mechanism for its formation.





Charles D. Winters

Breads, grains, and pasta are sources of carbohydrates. Inset: A model of glucose, the most abundant carbohydrate in nature.

Carbohydrates

17

KEY QUESTIONS

HOW TO

CHEMICAL CONNECTIONS

17.1 What Are Carbohydrates?

Carbohydrates are the most abundant organic compounds in the plant world. They act as storehouses of chemical energy (glucose, starch, glycogen); are components of supportive structures in plants (cellulose), crustacean shells (chitin), and connective tissues in animals (acidic polysaccharides); and are essential components of DNA and RNA (D-ribose and 2-deoxy-D-ribose). Carbohydrates account for approximately three-fourths of the dry weight of plants. Animals (including humans) get their carbohydrates by eating plants, but they do not store much of what they consume. In fact, less than 1% of the body weight of animals is made up of carbohydrates.

The word *carbohydrate* means "hydrate of carbon" and derives from the formula $C_n(H_2O)_m$. Two examples of carbohydrates with molecular formulas that can be written alternatively as hydrates of carbon are

- glucose (blood sugar), $C_6H_{12}O_6$, which can be written as $C_6(H_2O)_6$, and
- sucrose (table sugar), $C_{12}H_{22}O_{11}$, which can be written as $C_{12}(H_2O)_{11}$.

Not all carbohydrates, however, have this general formula. Some contain too few oxygen atoms to fit the formula, whereas some contain too many. Some also contain nitrogen. But

Cholesterol 0mg	**0%**	**0%**
Sodium 50mg	**2%**	**5%**
Total Carbohydrate 37g	**12%**	**14%**
Dietary Fiber 3g	**12%**	**12%**
Sugars 13g		
Protein 4g	**8%**	**16%**

Carbohydrate content is listed on all food labels in the U.S.

the term *carbohydrate* has become firmly rooted in chemical nomenclature and, although not completely accurate, it persists as the name for this class of compounds.

Carbohydrate A polyhydroxyaldehyde or polyhydroxyketone or a substance that gives these compounds on hydrolysis.

At the molecular level, most **carbohydrates** are polyhydroxyaldehydes, polyhydroxyketones, or compounds that yield them after hydrolysis. Therefore, the chemistry of carbohydrates is essentially the chemistry of hydroxyl and carbonyl groups and of acetal bonds (Section 12.6A) formed between these two functional groups.

17.2 What Are Monosaccharides?

A. Structure and Nomenclature

Monosaccharide A carbohydrate that cannot be hydrolyzed to a simpler compound.

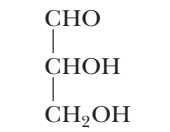
Aldose A monosaccharide containing an aldehyde group.

Ketose A monosaccharide containing a ketone group.

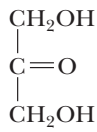
Monosaccharides have the general formula $C_nH_{2n}O_n$, with one of the carbons being the carbonyl group of either an aldehyde or a ketone. The most common monosaccharides have from three to nine carbon atoms. The suffix *-ose* indicates that a molecule is a carbohydrate, and the prefixes *tri-*, *tetr-*, *pent-*, and so forth, indicate the number of carbon atoms in the chain. Monosaccharides containing an aldehyde group are classified as **aldoses**; those containing a ketone group are classified as **ketoses**.

There are only two **trioses**—glyceraldehyde, which is an aldotriose, and dihydroxyacetone, which is a ketotriose:

"aldotriose" classifies the compound as an aldehyde (aldo) containing 3 carbons (tri) while being a carbohydrate (ose)



Glyceraldehyde (an aldotriose)



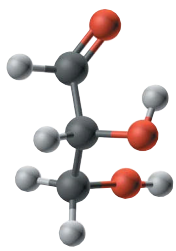
Dihydroxyacetone (a ketotriose)

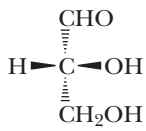
"ketotriose" classifies the compound as a ketone (keto) containing 3 carbons (tri) while being a carbohydrate (ose)

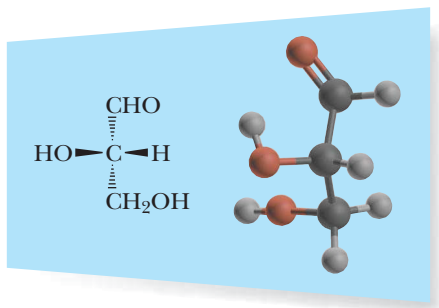
Often the designations *aldo-* and *keto-* are omitted, and these molecules are referred to simply as trioses, **tetroses**, and the like. Although these designations do not tell the nature of the carbonyl group, at least they indicate that the monosaccharide contains three and four carbon atoms, respectively.

B. Stereoisomerism

Glyceraldehyde contains one stereocenter and exists as a pair of enantiomers. The stereoisomer shown on the left has the *R* configuration and is named (*R*)-glyceraldehyde, while its enantiomer, shown on the right, is named (*S*)-glyceraldehyde:







(*R*)-Glyceraldehyde

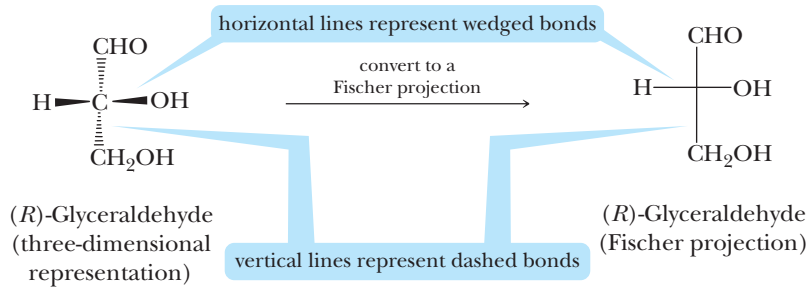
(*S*)-Glyceraldehyde

Fischer projection A two-dimensional representation showing the configuration of a stereocenter; horizontal lines represent bonds projecting forward from the stereocenter, whereas vertical lines represent bonds projecting to the rear. The stereocenter is the only atom in the plane.

C. Fischer Projection Formulas

Chemists commonly use two-dimensional representations called **Fischer projections** to show the configuration of carbohydrates. To draw a Fischer projection, draw a three-dimensional representation with the most oxidized carbon toward the top and the molecule oriented so

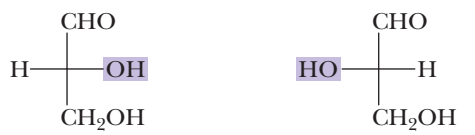
that the vertical bonds from the stereocenter are directed away from you and the horizontal bonds from it are directed toward you. Then write the molecule as a two-dimensional figure with the stereocenter indicated by the point at which the bonds cross. You now have a Fischer projection.



The two horizontal segments of this Fischer projection represent bonds directed toward you, and the two vertical segments represent bonds directed away from you. The only atom in the plane of the paper is the stereocenter.

D. D- and L-Monosaccharides

Even though the *R*, *S* system is widely accepted today as a standard for designating the configuration of stereocenters, we still commonly designate the configuration of carbohydrates by the D, L system proposed by Emil Fischer in 1891. He assigned the dextrorotatory and levorotary enantiomers of glyceraldehyde the following configurations and named them D-glyceraldehyde and L-glyceraldehyde, respectively:



D-Glyceraldehyde
$[\alpha]_D^{25} = +13.5°$

L-Glyceraldehyde
$[\alpha]_D^{25} = -13.5°$

D-glyceraldehyde and L-glyceraldehyde serve as reference points for the assignment of relative configurations to all other aldoses and ketoses. The reference point is the stereocenter farthest from the carbonyl group. Because this stereocenter is the next-to-the-last carbon on the chain, it is called the **penultimate carbon**. A **D-monosaccharide** is a monosaccharide that has the same configuration at its penultimate carbon as D-glyceraldehyde (its —OH is on the right in a Fischer projection); an **L-monosaccharide** has the same configuration at its penultimate carbon as L-glyceraldehyde (its —OH is on the left in a Fischer projection). Almost all monosaccharides in the biological world belong to the D series, and the majority of them are either **hexoses** or **pentoses**.

Penultimate carbon The stereocenter of a monosaccharide farthest from the carbonyl group—for example, carbon 5 of glucose.

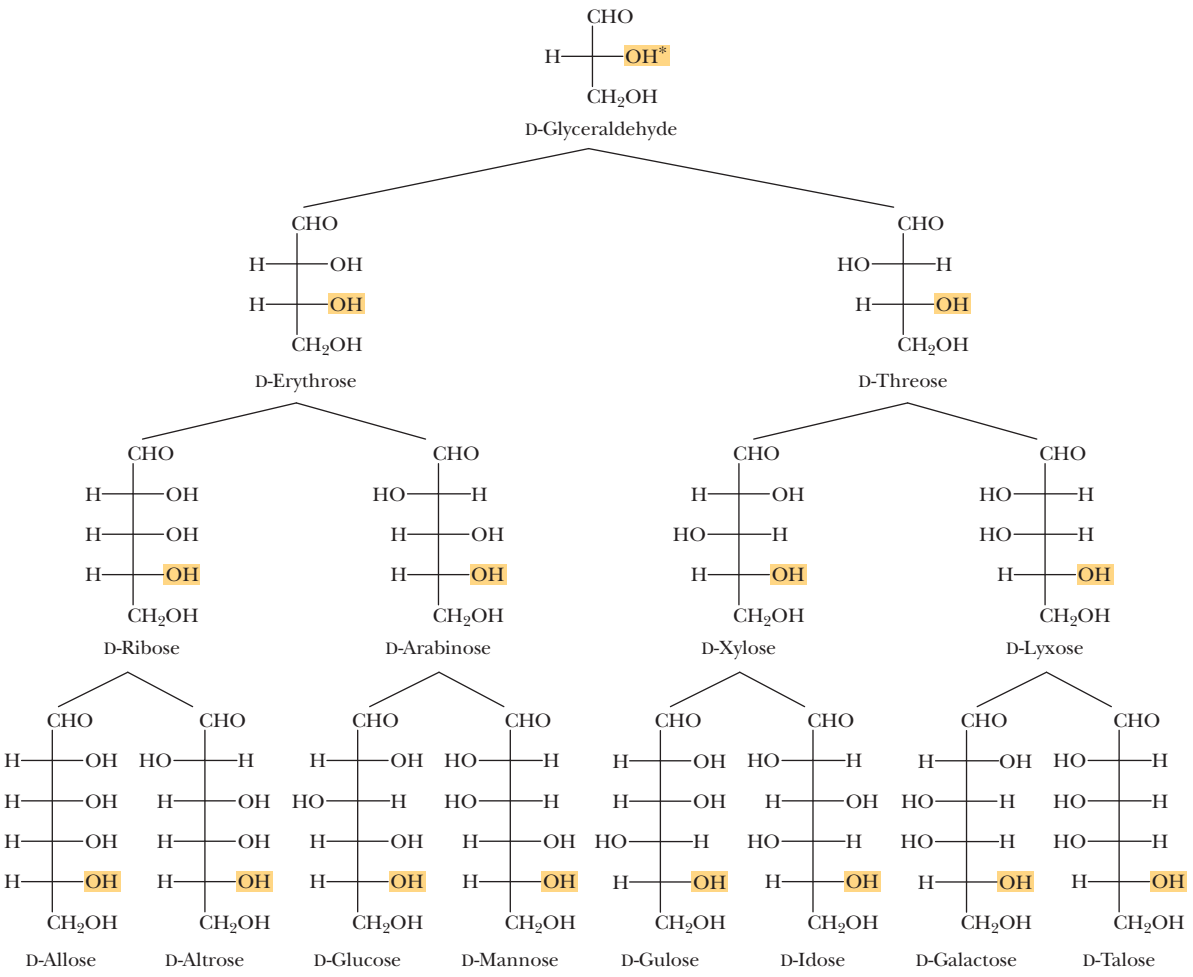
D-Monosaccharide A monosaccharide that, when written as a Fischer projection, has the —OH on its penultimate carbon to the right.

L-Monosaccharide A monosaccharide that, when written as a Fischer projection, has the —OH on its penultimate carbon to the left.

Table 17.1 shows the names and Fischer projection formulas for all D-aldotrioses, tetroses, pentoses, and hexoses. Each name consists of three parts. The letter D specifies the configuration at the stereocenter farthest from the carbonyl group. Prefixes, such as *rib-*, *arabin-*, and *gluc-*, specify the configurations of all other stereocenters relative to one another. The suffix *-ose* shows that the compound is a carbohydrate.

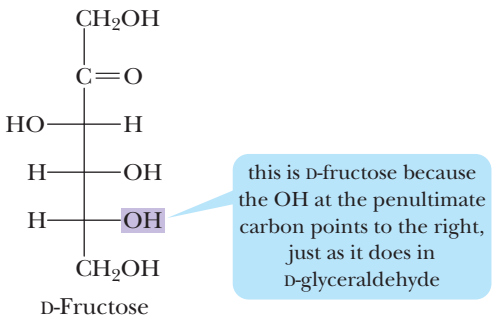
The three most abundant hexoses in the biological world are D-glucose, D-galactose, and D-fructose. The first two are D-aldohexoses; the third, fructose, is a D-2-ketohexose. Glucose, by far the most abundant of the three, is also known as dextrose because it is dextrorotatory. Other names for this monosaccharide include *grape sugar* and *blood sugar*. Human blood normally contains 65–110 mg of glucose/100 mL of blood.

TABLE 17.1 Configurational Relationships Among the Isomeric D-Aldotetroses, D-Aldopentoses, and D-Aldohexoses



*The configuration of the reference —OH on the penultimate carbon is shown in color.

D-Fructose is one of the two monosaccharide building blocks of sucrose (table sugar, Section 17.5):



EXAMPLE 17.1

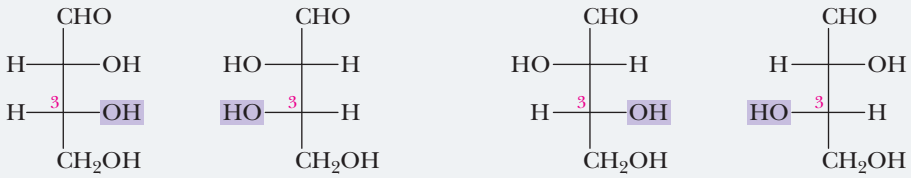
(a) Draw Fischer projections for the four aldotetroses.
(b) Which of the four aldotetroses are D-monosaccharides, which are L-monosaccharides, and which are enantiomers?
(c) Refer to Table 17.1, and name each aldotetrose you have drawn.

STRATEGY

Start with the Fischer projection of glyceraldehyde (a triose) and add one more carbon to the chain to give a tetrose. Carbon-1 of an aldotetrose is an aldehyde (as in glyceraldehyde) and carbon 4 is a CH_2OH. The designations D- and L- refer to the configuration of the penultimate carbon, which in the case of a tetrose is carbon 3. In the Fischer projection of a D-aldotetrose, the —OH group on carbon 3 is on the right and in an L-aldotetrose, it is on the left.

SOLUTION

Following are Fischer projections for the four aldotetroses:



D-Erythrose | L-Erythrose (one pair of enantiomers)

D-Threose | L-Threose (a second pair of enantiomers)

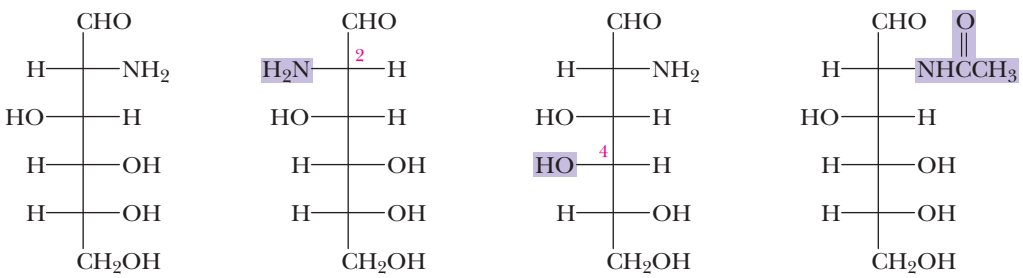
See problems 17.13, 17.14

PROBLEM 17.1

(a) Draw Fischer projections for all 2-ketopentoses.
(b) Which of the 2-ketopentoses are D-ketopentoses, which are L-ketopentoses, and which are enantiomers?

E. Amino Sugars

Amino sugars contain an $—NH_2$ group in place of an —OH group. Only three amino sugars are common in nature: D-glucosamine, D-mannosamine, and D-galactosamine. *N*-Acetyl-D-glucosamine, a derivative of D-glucosamine, is a component of many polysaccharides, including connective tissue such as cartilage. It is also a component of chitin, the hard shell-like exoskeleton of lobsters, crabs, shrimp, and other shellfish. Several other amino sugars are components of naturally occurring antibiotics.



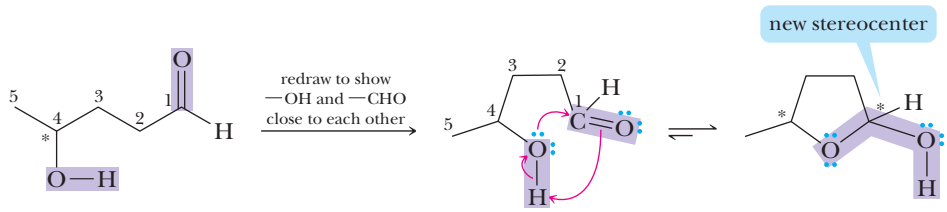
D-Glucosamine | D-Mannosamine (C-2 stereoisomer of D-glucosamine) | D-Galactosamine (C-4 stereoisomer of D-glucosamine) | *N*-Acetyl-D-glucosamine

F. Physical Properties

Monosaccharides are colorless, crystalline solids. Because hydrogen bonding is possible between their polar —OH groups and water, all monosaccharides are very soluble in water. They are only slightly soluble in ethanol and are insoluble in nonpolar solvents such as diethyl ether, dichloromethane, and benzene.

17.3 What Are the Cyclic Structures of Monosaccharides?

In Section 12.6, we saw that aldehydes and ketones react with alcohols to form **hemiacetals**. We also saw that cyclic hemiacetals form very readily when hydroxyl and carbonyl groups are parts of the same molecule and their interaction can form a five- or six-membered ring. For example, 4-hydroxypentanal forms a five-membered cyclic hemiacetal. Note that 4-hydroxypentanal contains one stereocenter and that a second stereocenter is generated at carbon 1 as a result of hemiacetal formation:



4-Hydroxypentanal A cyclic hemiacetal

Because monosaccharides have hydroxyl and carbonyl groups in the same molecule, they exist almost exclusively as five- and six-membered cyclic hemiacetals.

A. Haworth Projections

Haworth projection A way of viewing the furanose and pyranose forms of monosaccharides. The ring is drawn flat and viewed through its edge, with the anomeric carbon on the right and the oxygen atom of the ring in the rear to the right.

Anomeric carbon The hemiacetal carbon of the cyclic form of a monosaccharide.

Anomers Monosaccharides that differ in configuration only at their anomeric carbons.

A common way of representing the cyclic structure of monosaccharides is the **Haworth projection**, named after the English chemist Sir Walter N. Haworth, Nobel laureate of 1937. In a Haworth projection, a five- or six-membered cyclic hemiacetal is represented as a planar pentagon or hexagon, respectively, lying roughly perpendicular to the plane of the paper. Groups bonded to the carbons of the ring then lie either above or below the plane of the ring. The new stereocenter created in forming the cyclic hemiacetal is called the **anomeric carbon**. Stereoisomers that differ in configuration only at the anomeric carbon are called **anomers**. The anomeric carbon of an aldose is carbon 1; in D-fructose, the most common ketose, it is carbon 2.

Typically, Haworth projections are written with the anomeric carbon at the right and the hemiacetal oxygen at the back right (Figure 17.1).

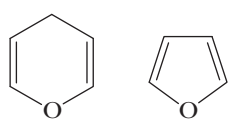
As you study the open chain and cyclic hemiacetal forms of D-glucose, note that, in converting from a Fischer projection to a Haworth structure,

- Groups on the right in the Fischer projection point down in the Haworth projection.
- Groups on the left in the Fischer projection point up in the Haworth projection.
- For a D-monosaccharide, the terminal —CH_2OH points up in the Haworth projection.
- The configuration of the anomeric —OH group is relative to the terminal —CH_2OH group: If the anomeric —OH group is on the same side as the terminal —CH_2OH, its configuration is β; if the anomeric —OH group is on the opposite side, it is α.

Furanose A five-membered cyclic hemiacetal form of a monosaccharide.

Pyranose A six-membered cyclic hemiacetal form of a monosaccharide.

A six-membered hemiacetal ring is shown by the infix **-pyran-**, and a five-membered hemiacetal ring is shown by the infix **-furan-**. The terms **furanose** and **pyranose** are used because monosaccharide five- and six-membered rings correspond to the heterocyclic compounds pyran and furan:



Pyran Furan

Because the α and β forms of glucose are six-membered cyclic hemiacetals, they are named α-D-glucopyranose and β-D-glucopyranose, respectively. The designations *-furan-* and

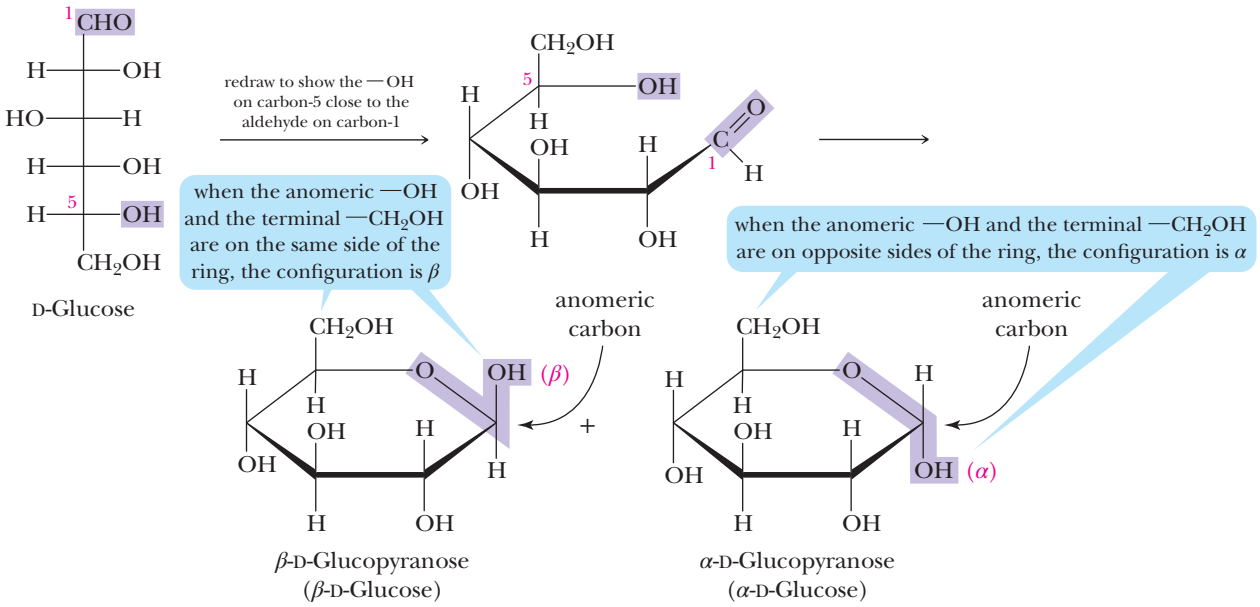


FIGURE 17.1 Haworth projections for β-D-glucopyranose and α-D-glucopyranose.

-pyran- are not always used, however, in names of monosaccharides. Thus, the glucopyranoses are often named simply α-D-glucose and β-D-glucose.

You would do well to remember the configuration of groups on the Haworth projection of both α-D-glucopyranose and β-D-glucopyranose as reference structures. Knowing how the Fischer projection of any other monosaccharide differs from that of D-glucose, you can then construct the Haworth projection of that other monosaccharide by reference to the Haworth projection of D-glucose.

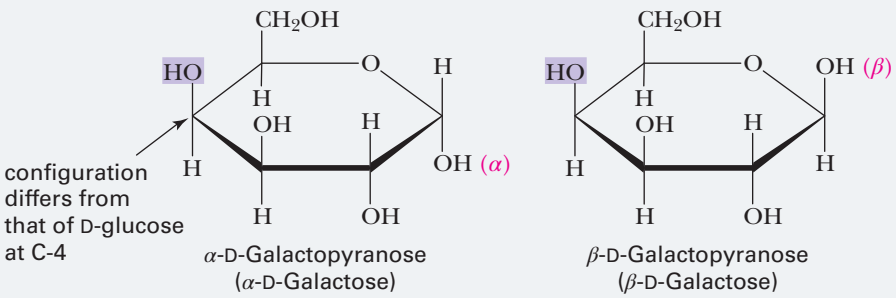
EXAMPLE 17.2

Draw Haworth projections for the α and β anomers of D-galactopyranose.

STRATEGY

One way to arrive at the structures for the α and β anomers of D-galactopyranose is to use the α and β forms of D-glucopyranose as a reference and to remember (or discover by looking at Table 17.1) that D-galactose differs from D-glucose only in the configuration at carbon 4. Thus, you can begin with the Haworth projections shown in Figure 17.1 and then invert the configuration at carbon 4.

SOLUTION

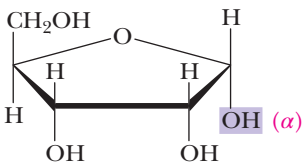


See problems 17.23, 17.26

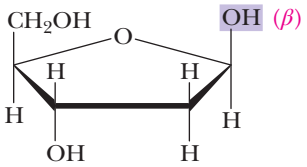
PROBLEM 17.2

Mannose exists in aqueous solution as a mixture of α-D-mannopyranose and β-D-mannopyranose. Draw Haworth projections for these molecules.

Aldopentoses also form cyclic hemiacetals. The most prevalent forms of D-ribose and other pentoses in the biological world are furanoses. Following are Haworth projections for α-D-ribofuranose (α-D-ribose) and β-2-deoxy-D-ribofuranose (β-2-deoxy-D-ribose):



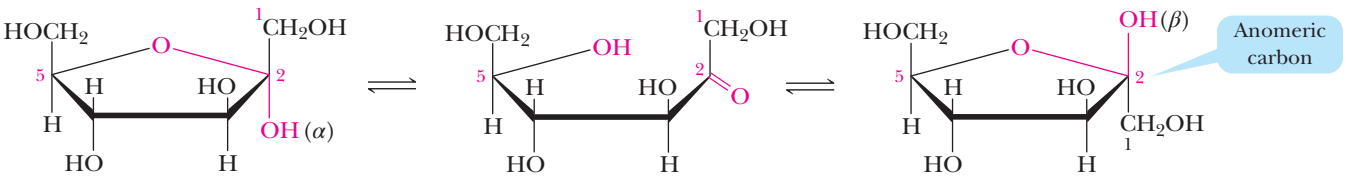
α-D-Ribofuranose
(α-D-Ribose)



β-2-Deoxy-D-ribofuranose
(β-2-Deoxy-D-ribose)

The prefix 2-deoxy indicates the absence of oxygen at carbon 2. Units of D-ribose and 2-deoxy-D-ribose in nucleic acids and most other biological molecules are found almost exclusively in the β-configuration.

Fructose also forms five-membered cyclic hemiacetals. β-D-Fructofuranose, for example, is found in the disaccharide sucrose (Section 17.5A).



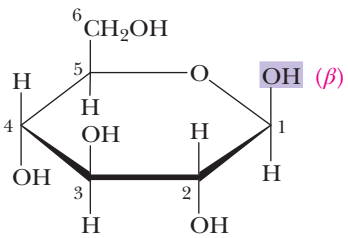
α-D-Fructofuranose
(α-D-Fructose)

β-D-Fructofuranose
(β-D-Fructose)

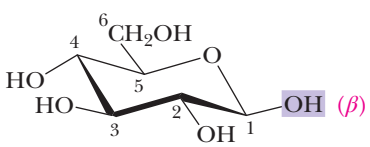
B. Chair Conformation Representations

A five-membered ring is so close to being planar that Haworth projections are adequate to represent furanoses. For pyranoses, however, the six-membered ring is more accurately represented as a **chair conformation** in which strain is a minimum (Section 3.6B). Figure 17.2 shows structural formulas for α-D-glucopyranose and β-D-glucopyranose, both drawn as chair conformations. The figure also shows the open-chain, or free, aldehyde form with which the cyclic hemiacetal forms are in equilibrium in aqueous solution. Notice that each group, including the anomeric —OH, on the chair conformation of β-D-glucopyranose is equatorial. Notice also that the —OH group on the anomeric carbon in α-D-glucopyranose is axial. Because of the equatorial orientation of the —OH on its anomeric carbon, β-D-glucopyranose is more stable than the α-anomer and therefore predominates in aqueous solution.

At this point, you should compare the relative orientations of groups on the D-glucopyranose ring in the Haworth projection and chair conformation:



β-D-Glucopyranose
(Haworth projection)



β-D-Glucopyranose
(chair conformation)

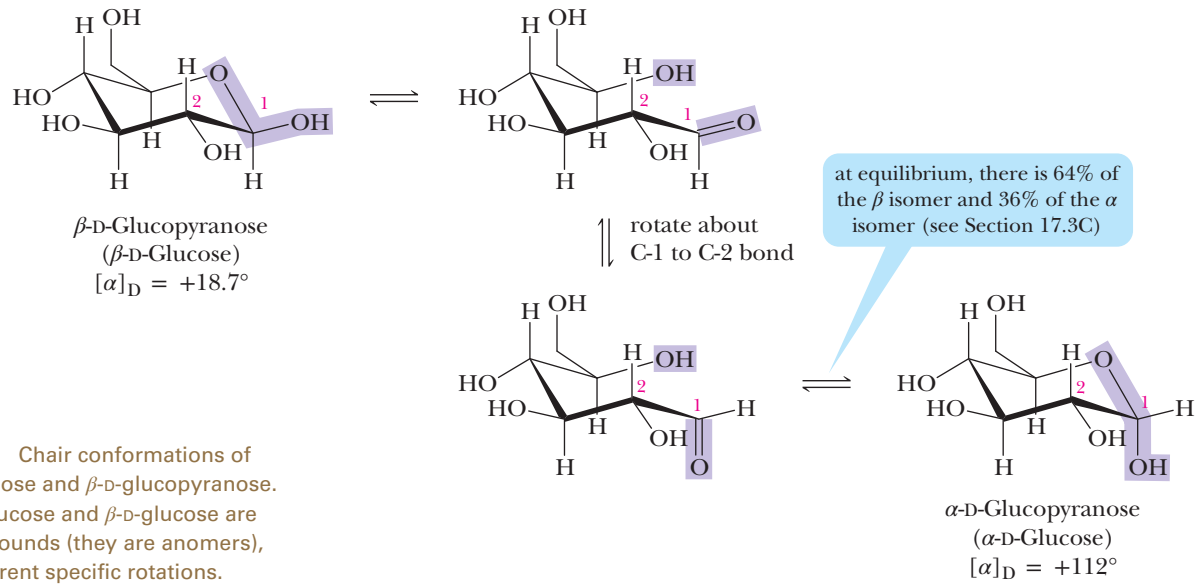


FIGURE 17.2 Chair conformations of α-D-glucopyranose and β-D-glucopyranose. Because α-D-glucose and β-D-glucose are different compounds (they are anomers), they have different specific rotations.

Notice that the orientations of groups on carbons 1 through 5 in the Haworth projection of β-D-glucopyranose are up, down, up, down, and up, respectively. The same is the case in the chair conformation.

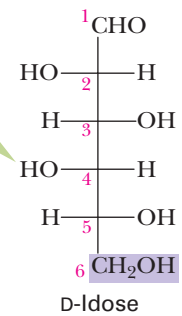
Determine the Stereochemistry of OH Groups in Cyclic D-Monosaccharides

HOW TO 17.1

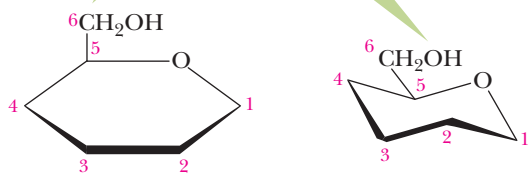
There is another way to determine the stereochemistry of OH groups in the D-series of monosaccharides if you forget the structure of glucopyranose:

(a) Draw the Haworth or chair form of the ring and number the corresponding carbon atoms (don't forget to situate the ring oxygen in the correct position):

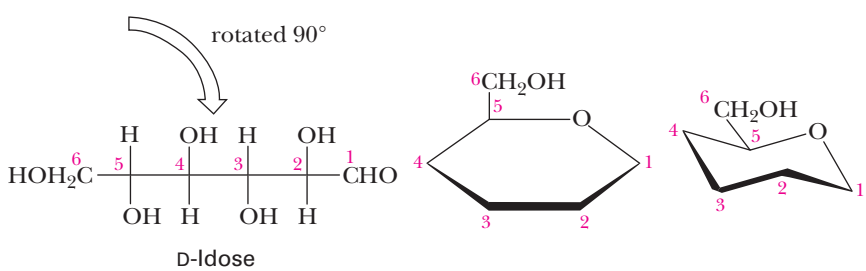
idose does not exist in nature, but its C-6 oxidized analog, iduronic acid does and is an important component in biological systems



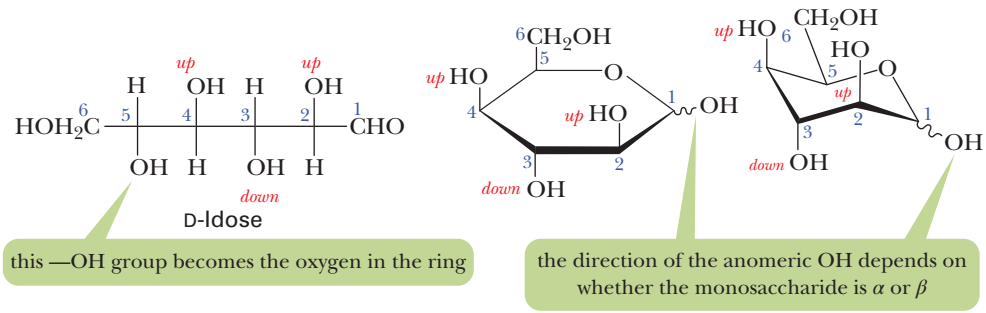
the CH_2OH group is always "up" in D-monosaccharides



(b) Rotate the drawing of the acyclic monosaccharide clockwise by 90°:



(c) The direction (up or down) of the OH group on the rotated structure is the direction the OH group should be on the cyclic monosaccharide:



EXAMPLE 17.3

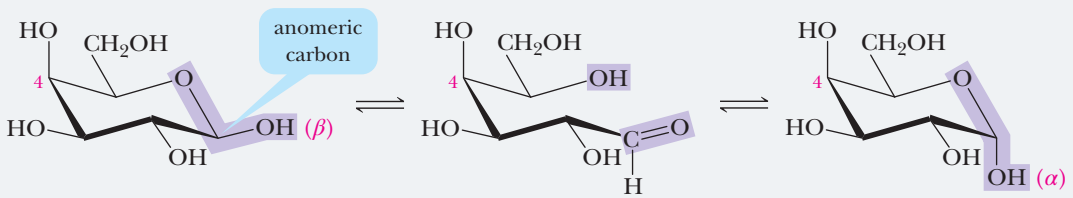
Draw chair conformations for α-D-galactopyranose and β-D-galactopyranose. Label the anomeric carbon in each cyclic hemiacetal.

STRATEGY

The configuration of D-galactose differs from that of D-glucose only at carbon 4. Therefore, draw the α and β forms of D-glucopyranose and then interchange the positions of the —OH and —H groups on carbon 4.

SOLUTION

Shown are the requested α and β forms of D-galactose. Also shown are the specific rotations of each anomer.



β-D-Galactopyranose (β-D-Galactose) $[\alpha]_D = +52.8°$

D-Galactose

α-D-Galactopyranose (α-D-Galactose) $[\alpha]_D = +150.7°$

See problem 17.26

PROBLEM 17.3

Draw chair conformations for α-D-mannopyranose and β-D-mannopyranose. Label the anomeric carbon atom in each.

C. Mutarotation

Mutarotation The change in optical activity that occurs when an α or β form of a carbohydrate is converted to an equilibrium mixture of the two forms.

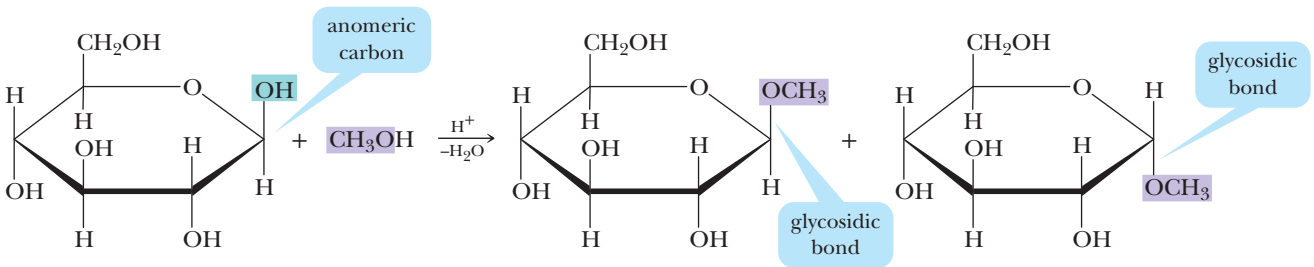
Mutarotation is the change in specific rotation that accompanies the interconversion of α- and β-anomers in aqueous solution. As an example, a solution prepared by dissolving crystalline α-D-glucopyranose in water shows an initial rotation of +112° (Figure 17.2), which gradually decreases to an equilibrium value of +52.7° as α-D-glucopyranose reaches an equilibrium with β-D-glucopyranose. A solution of β-D-glucopyranose also undergoes mutarotation, during which the specific rotation changes from an initial value of +18.7° to the same equilibrium value of +52.7°. The equilibrium mixture consists of 64% β-D-glucopyranose and 36% α-D-glucopyranose and contains only traces (0.003%) of the open-chain form. Mutarotation is common to all carbohydrates that exist in hemiacetal forms.

17.4 What Are the Characteristic Reactions of Monosaccharides?

In this section, we discuss reactions of monosaccharides with alcohols, reducing agents, and oxidizing agents. In addition, we examine how these reactions are useful in our everyday lives.

A. Formation of Glycosides (Acetals)

As we saw in Section 12.6A, treating an aldehyde or a ketone with one molecule of alcohol yields a hemiacetal, and treating the hemiacetal with a molecule of alcohol yields an acetal. Treating a monosaccharide, all forms of which exist as cyclic hemiacetals, with an alcohol gives an acetal, as illustrated by the reaction of β-D-glucopyranose (β-D-glucose) with methanol:



A cyclic acetal derived from a monosaccharide is called a **glycoside**, and the bond from the anomeric carbon to the —OR group is called a **glycosidic bond**. Mutarotation is no longer possible in a glycoside because, unlike a hemiacetal, an acetal is no longer in equilibrium with the open-chain carbonyl-containing compound in neutral or alkaline solution. Like other acetals (Section 12.6), glycosides are stable in water and aqueous base, but undergo hydrolysis in aqueous acid to an alcohol and a monosaccharide.

Glycoside A carbohydrate in which the —OH on its anomeric carbon is replaced by —OR.

Glycosidic bond The bond from the anomeric carbon of a glycoside to an —OR group.

We name glycosides by listing the alkyl or aryl group bonded to oxygen, followed by the name of the carbohydrate involved in which the ending **-e** is replaced by **-ide**. For example, glycosides derived from β-D-glucopyranose are named β-D-glucopyranosides; those derived from β-D-ribofuranose are named β-D-ribofuranosides.

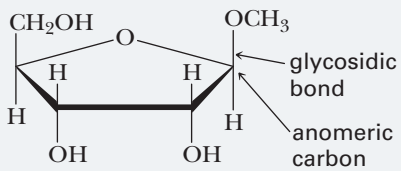
EXAMPLE 17.4

Draw a structural formula for methyl β-D-ribofuranoside (methyl β-D-riboside). Label the anomeric carbon and the glycosidic bond.

STRATEGY

Furanosides are five-membered cyclic acetals. The anomeric carbon is carbon 1, and the glycosidic bond is formed to carbon 1. For a β-glycosidic bond, the —OR group is above the plane of the ring and on the same side as the terminal —CH_2OH group (carbon 5 of a furanoside).

SOLUTION



See problems 17.30–17.32

PROBLEM 17.4

Draw a structural formula for the chair conformation of methyl α-D-mannopyranoside (methyl α-D-mannoside). Label the anomeric carbon and the glycosidic bond.

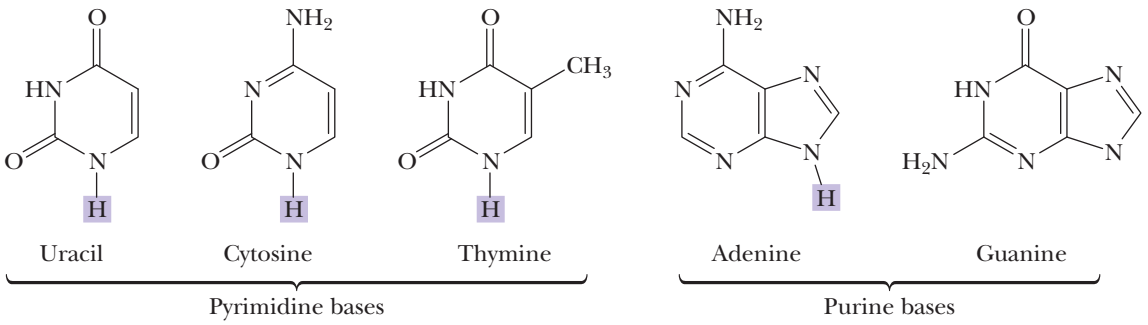


FIGURE 17.3 Structural formulas of the five most important purine and pyrimidine bases found in DNA and RNA. The hydrogen atom shown in color is lost in the formation of an *N*-glycoside.

Just as the anomeric carbon of a cyclic hemiacetal undergoes reaction with the —OH group of an alcohol to form a glycoside, it also undergoes reaction with the —NH group of an amine to form an *N*-glycoside. Especially important in the biological world are the *N*-glycosides formed between D-ribose and 2-deoxy-D-ribose (each as a furanose), and the heterocyclic aromatic amines uracil, cytosine, thymine, adenine, and guanine (Figure 17.3). *N*-Glycosides of these compounds are structural units of nucleic acids (Chapter 20).

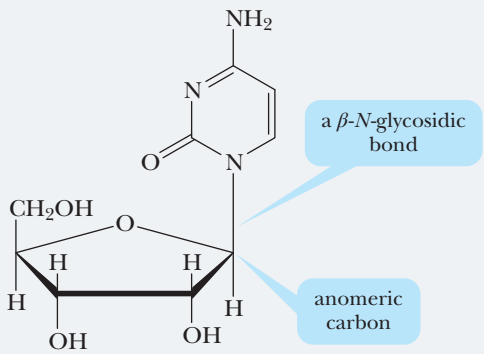
EXAMPLE 17.5

Draw a structural formula for the β-*N*-glycoside formed between D-ribofuranose and cytosine. Label the anomeric carbon and the *N*-glycosidic bond.

STRATEGY

Start with the Haworth projection of β-D-ribofuranose. Locate the anomeric carbon (carbon 1). Remove the —OH group from carbon 1 and in its place, bond the appropriate nitrogen atom of cytosine (see Figure 17.3) to give the β-*N*-glycosidic bond.

SOLUTION



See problem 17.33

PROBLEM 17.5

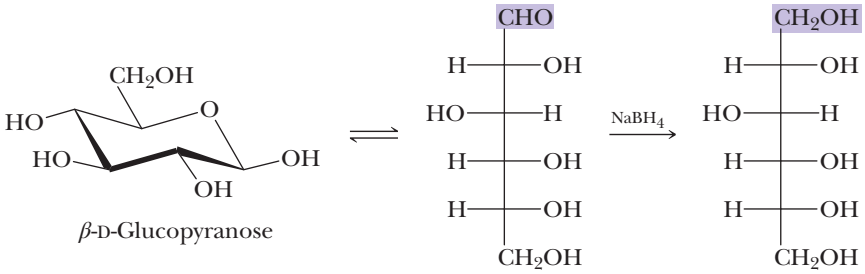
Draw a structural formula for the β-*N*-glycoside formed between β-D-ribofuranose and adenine.

B. Reduction to Alditols

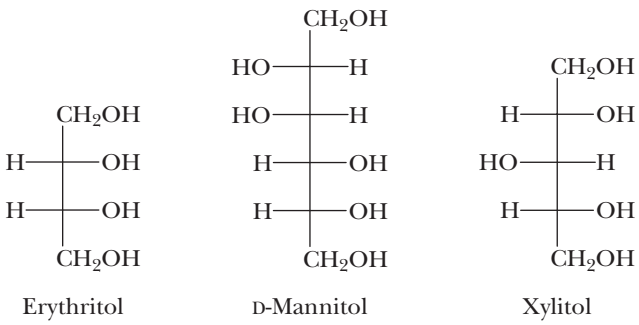
Alditol The product formed when the C=O group of a monosaccharide is reduced to a CHOH group.

The carbonyl group of a monosaccharide can be reduced to a hydroxyl group by a variety of reducing agents, including $NaBH_4$ (Section 12.10B). The reduction products are known as **alditols**. Reduction of D-glucose gives D-glucitol, more commonly known as D-sorbitol. Here, D-glucose is shown in the open-chain form, only a small amount of which is present in solution, but, as it is reduced, the equilibrium between the cyclic hemiacetal forms and

the open-chain form shifts to replace the D-glucose (see Problem 17.65 for the biological analog of this reaction):



We name alditols by replacing the *-ose* in the name of the monosaccharide with *-itol*. D-Sorbitol is found in the plant world in many berries and in cherries, plums, pears, apples, seaweed, and algae. It is about 60% as sweet as sucrose (table sugar) and is used in the manufacture of candies and as a sugar substitute for diabetics. Among other alditols common in the biological world are erythritol, D-mannitol, and xylitol, the last of which is used as a sweetening agent in "sugarless" gum, candy, and sweet cereals:



Andy Washnik

Many "sugar-free" products contain sugar alcohols, such as D-sorbitol and xylitol.

EXAMPLE 17.6

$NaBH_4$ reduces D-glucose to D-glucitol. Do you expect the alditol formed under these conditions to be optically active or optically inactive? Explain.

STRATEGY

$NaBH_4$ reduces the aldehyde group (—CHO) of D-glucose to a primary alcohol (—CH_2OH). Reduction does not affect any other group in D-glucose. The problem then is to determine if D-glucitol is chiral and, if it is chiral, to see whether it has a plane of symmetry, in which case it would be superposable on its mirror image and, therefore, optically inactive.

SOLUTION

D-Glucitol does not have a plane of symmetry and is chiral. Therefore, we predict that D-glucitol is optically active. Its specific rotation is –1.7°.

See problems 17.34–17.39

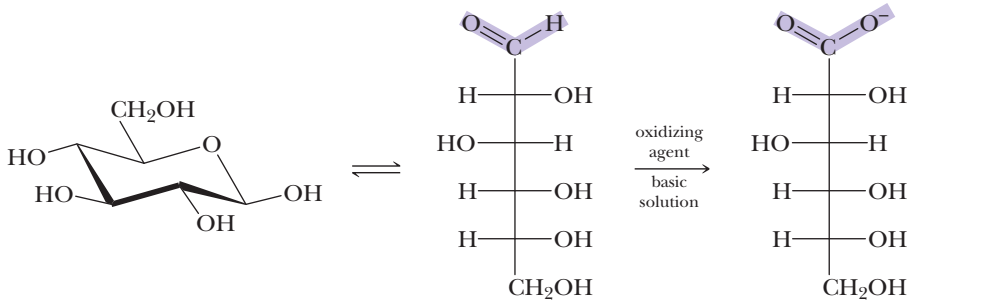
PROBLEM 17.6

$NaBH_4$ reduces D-erythrose to erythritol. Do you expect the alditol formed under these conditions to be optically active or optically inactive? Explain.

C. Oxidation to Aldonic Acids (Reducing Sugars)

We saw in Section 12.9A that several agents, including O_2, oxidize aldehydes (RCHO) to carboxylic acids (RCOOH). Similarly, under basic conditions, the aldehyde group of an aldose can be oxidized to a carboxylate group. Under these conditions, the cyclic form of the aldose

is in equilibrium with the open-chain form, which is then oxidized by the mild oxidizing agent. D-Glucose, for example, is oxidized to D-gluconate (the anion of D-gluconic acid):



β-D-Glucopyranose (β-D-Glucose) | D-Glucose | D-Gluconate (anion of an aldonic acid)

Reducing sugar A carbohydrate that reacts with an oxidizing agent to form an aldonic acid.

Any carbohydrate that reacts with an oxidizing agent to form an aldonic acid is classified as a **reducing sugar**. (It reduces the oxidizing agent.)

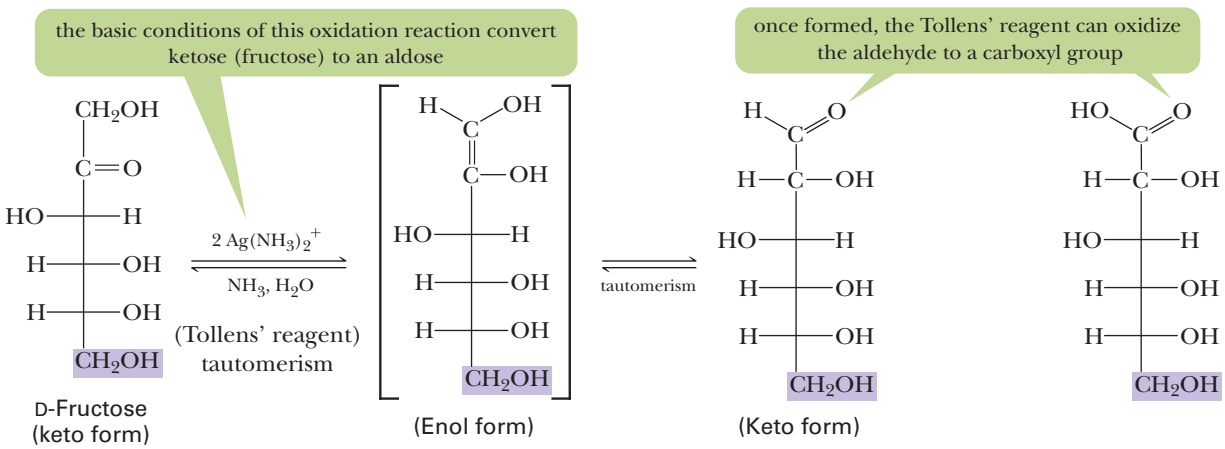
Determine If a Carbohydrate Is a Reducing Sugar

HOW TO 17.2

Following are three commonly encountered features in carbohydrates that are reducing sugars.

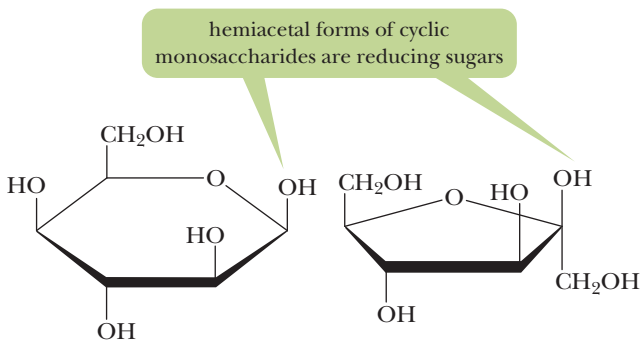
(1) Any carbohydrate that is an aldehyde is a reducing sugar.

(2) Any ketose that is in equilibrium with its aldehyde is a reducing sugar. This is because under the basic conditions of the Tollens' test, keto–enol tautomerism occurs and converts the ketose to an aldose (it is the aldose that is the actual reducing sugar):



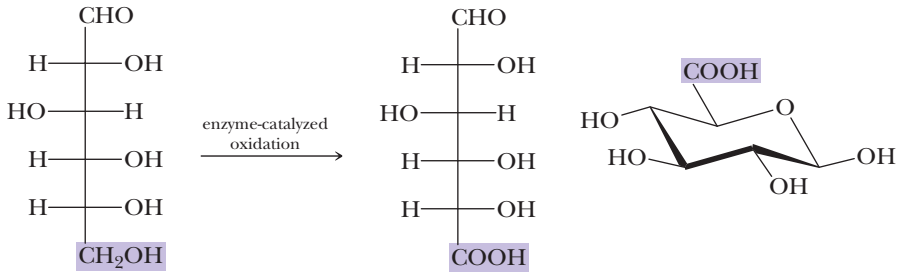
D-Fructose (keto form) | (Enol form) | (Keto form)

(3) Any ring carbohydrate that exists as a hemiacetal will be in equilibrium with its acyclic form. The acyclic form will either be an aldose or a 2-ketose, which under the conditions of the Tollens' test will be converted to an aldose (see #2 above). It is the aldose that is the actual reducing sugar:



D. Oxidation to Uronic Acids

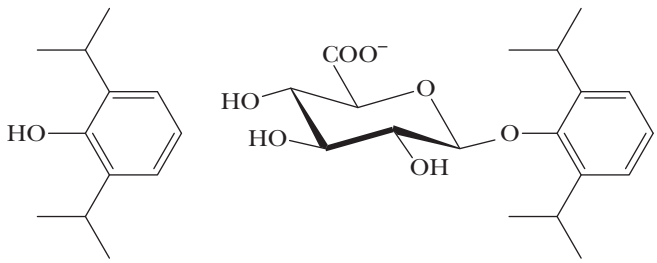
Enzyme-catalyzed oxidation of the primary alcohol at carbon 6 of a hexose yields a **uronic acid**. Enzyme-catalyzed oxidation of D-glucose, for example, yields D-glucuronic acid, shown here in both its open-chain and cyclic hemiacetal forms:



D-Glucose — Fischer projection — Chair conformation

D-Glucuronic acid
(a uronic acid)

D-Glucuronic acid is widely distributed in both the plant and animal worlds. In humans, it is an important component of the acidic polysaccharides of connective tissues. The body also uses it to detoxify foreign phenols and alcohols. In the liver, these compounds are converted to glycosides of glucuronic acid (glucuronides), to be excreted in the urine. The intravenous anesthetic propofol (Problem 10.43), for example, is converted to the following water-soluble glucuronide and then excreted in the urine:



Propofol — A urine-soluble glucuronide

17.5 What Are Disaccharides and Oligosaccharides?

Most carbohydrates in nature contain more than one monosaccharide unit. Those that contain two units are called **disaccharides**, those that contain three units are called **trisaccharides**, and so forth. The more general term, **oligosaccharide**, is often used for carbohydrates that contain from 6 to 10 monosaccharide units. Carbohydrates containing larger numbers of monosaccharide units are called **polysaccharides** (Section 17.6).

In a disaccharide, two monosaccharide units are joined by a glycosidic bond between the anomeric carbon of one unit and an —OH of the other. Sucrose, lactose, and maltose are three important disaccharides.

Disaccharide A carbohydrate containing two monosaccharide units joined by a glycosidic bond.

Oligosaccharide A carbohydrate containing from 6 to 10 monosaccharide units, each joined to the next by a glycosidic bond.

Polysaccharide A carbohydrate containing a large number of monosaccharide units, each joined to the next by one or more glycosidic bonds.

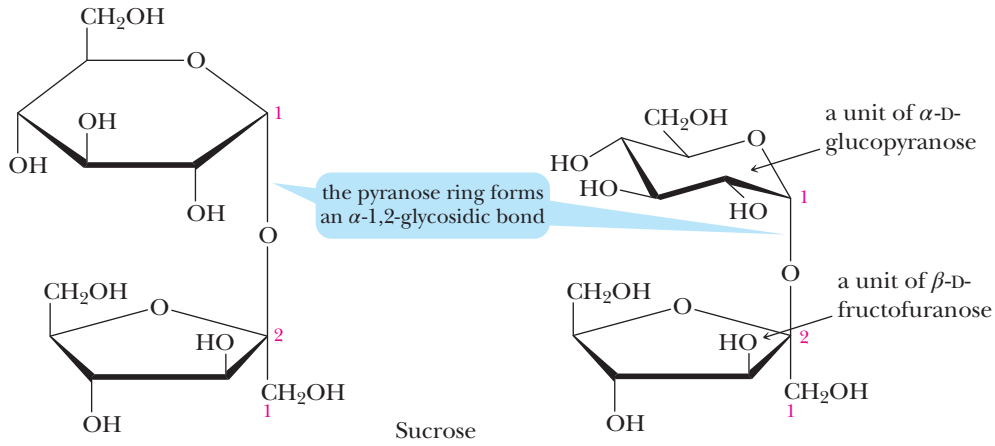
A. Sucrose

Sucrose (table sugar) is the most abundant disaccharide in the biological world. It is obtained principally from the juice of sugarcane and sugar beets. In sucrose, carbon 1

Charles D. Winters

These products help individuals with lactose intolerance meet their calcium needs.

of α-D-glucopyranose bonds to carbon 2 of D-fructofuranose by an α-1,2-glycosidic bond:

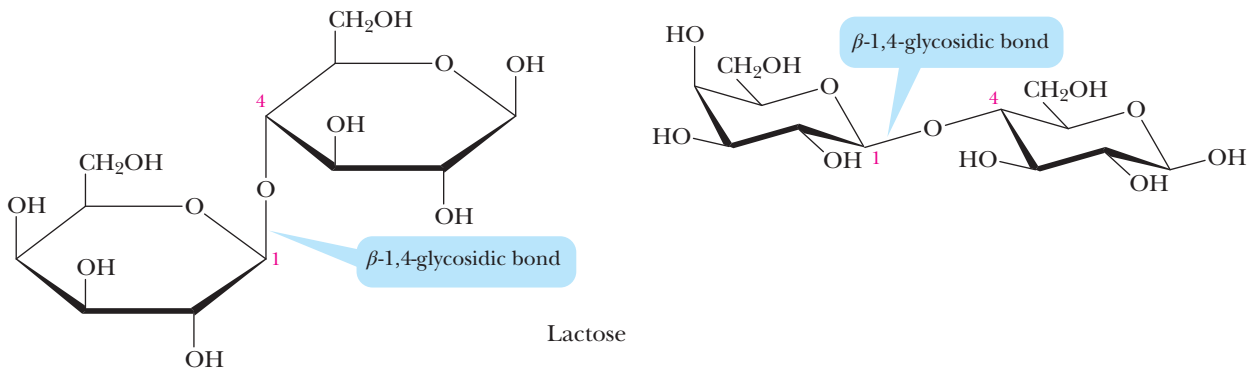


Sucrose

Because the anomeric carbons of both the glucopyranose and fructofuranose units are involved in formation of the glycosidic bond, neither monosaccharide unit is in equilibrium with its open-chain form. Thus, sucrose is a nonreducing sugar.

B. Lactose

Lactose, the principal sugar present in milk, accounts for 5 to 8% of human milk and 4 to 6% of cow's milk. This disaccharide consists of D-galactopyranose, bonded by a β-1,4-glycosidic bond to carbon 4 of D-glucopyranose:



Lactose

Lactose is a reducing sugar, because the cyclic hemiacetal of the D-glucopyranose unit is in equilibrium with its open-chain form and can be oxidized to a carboxyl group.

Chemical Connections 17A

RELATIVE SWEETNESS OF CARBOHYDRATE AND ARTIFICIAL SWEETENERS

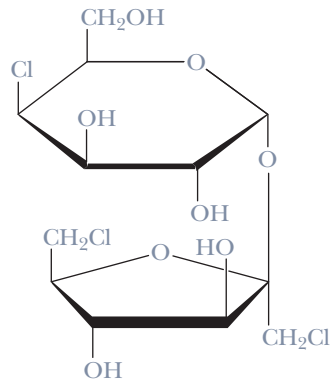
Among the disaccharide sweetening agents, D-fructose tastes the sweetest—even sweeter than sucrose. The sweet taste of honey is due largely to D-fructose and D-glucose. Lactose has almost no sweetness and is sometimes added to foods as filler. Some people cannot tolerate lactose well, however, and should

avoid these foods. The following table lists the sweetness of various carbohydrates and artificial sweeteners relative to that of sucrose:

Carbohydrate	Sweetness Relative to Sucrose	Artificial Sweetener	Sweetness Relative to Sucrose
Fructose	1.74	Saccharin	450
Sucrose (table sugar)	1.00	Acesulfame-K	200
Honey	0.97	Aspartame	180
Glucose	0.74	Sucralose	600
Maltose	0.33		
Galactose	0.32		
Lactose (milk sugar)	0.16		

Question

Following is the structure of the artificial sweetener sucralose. Indicate all the ways in which it differs from sucrose.



Sucralose

C. Maltose

Maltose derives its name from its presence in malt, the juice from sprouted barley and other cereal grains. Maltose consists of two units of D-glucopyranose, joined by a glycosidic bond between carbon 1 (the anomeric carbon) of one unit and carbon 4 of the other unit. Because the oxygen atom on the anomeric carbon of the first glucopyranose unit is alpha, the bond joining the two units is called an α-1,4-glycosidic bond. Following are a Haworth projection and a chair conformation for β-maltose, so named because the —OH group on the anomeric carbon of the glucose unit on the right is beta:

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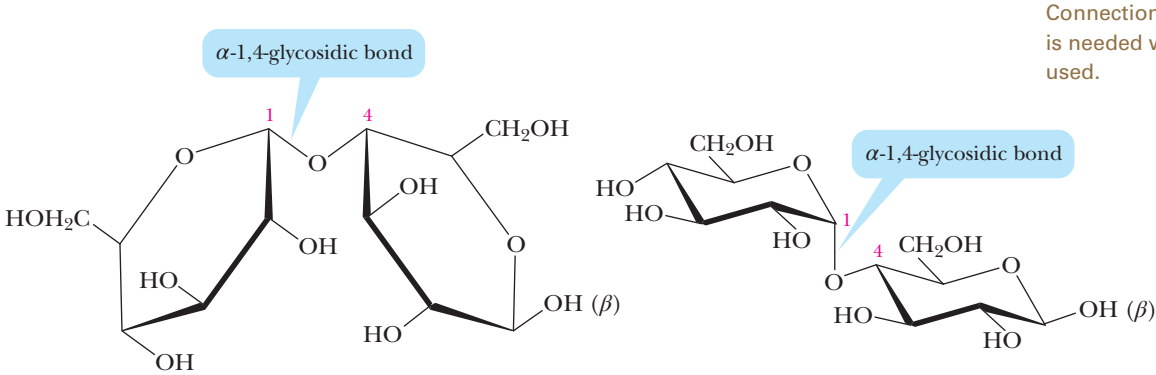
Because artificial sweeteners are much sweeter relative to table sugar (Chemical Connections 17A), much less is needed whenever they are used.



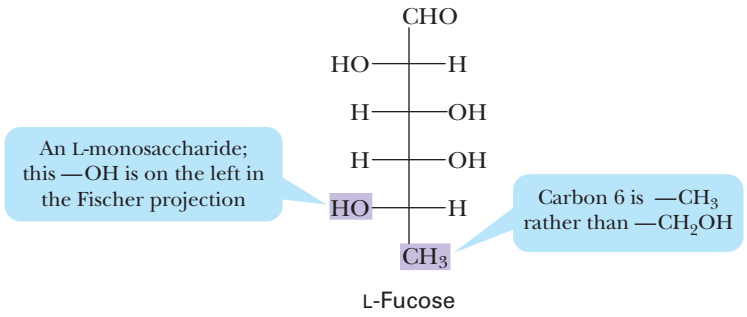
Maltose

Chemical Connections 17B

A, B, AB, AND O BLOOD-GROUP SUBSTANCES

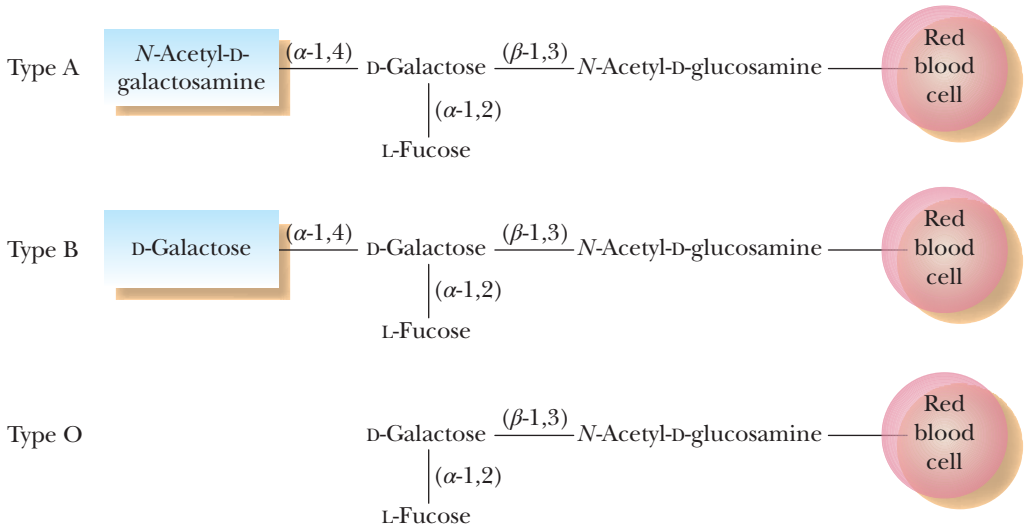
Membranes of animal plasma cells have large numbers of relatively small carbohydrates bound to them. In fact, the outsides of most plasma cell membranes are literally sugarcoated. These membrane-bound carbohydrates are part of the mechanism by which the different types of cells recognize each other; in effect, the carbohydrates act as biochemical markers (antigenic determinants). Typically, the membrane-bound carbohydrates contain from 4 to 17

units consisting of just a few different monosaccharides, primarily D-galactose, D-mannose, L-fucose, *N*-acetyl-D-glucosamine, and *N*-acetyl-D-galactosamine. L-Fucose is a 6-deoxyaldohexose:



L-Fucose

Among the first discovered and best understood of these membrane-bound carbohydrates are those of the ABO blood-group system, discovered in 1900 by Karl Landsteiner (1868–1943). Whether an individual has type A, B, AB, or O blood is genetically determined and depends on the type of trisaccharide or tetrasaccharide bound to the surface of the person's red blood cells. The monosaccharides of each blood group and the type of glycosidic bond joining them are shown in the following figure (the configurations of the glycosidic bonds are in parentheses):



Question

Draw the two pyranose forms of L-fucose.

EXAMPLE 17.7

Draw a chair conformation for the β anomer of a disaccharide in which two units of D-glucopyranose are joined by an α-1,6-glycosidic bond.

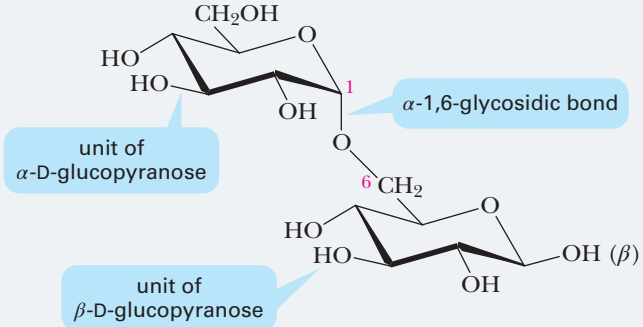
STRATEGY

First draw a chair conformation of α-D-glucopyranose. Then bond the anomeric carbon of this monosaccharide to carbon 6 of a second α-D-glucopyranose unit by an α-glycosidic bond. The resulting molecule is either α or β, depending on the orientation of the —OH group on the reducing end of the disaccharide.

See problem 17.48

SOLUTION

The disaccharide shown here is β:



PROBLEM 17.7

Draw Haworth and chair formulas for the α form of a disaccharide in which two units of D-glucopyranose are joined by a β-1,3-glycosidic bond.

17.6 What Are Polysaccharides?

Polysaccharides consist of a large number of monosaccharide units joined together by glycosidic bonds. Three important polysaccharides, all made up of glucose units, are starch, glycogen, and cellulose.

A. Starch: Amylose and Amylopectin

Starch is found in all plant seeds and tubers and is the form in which glucose is stored for later use. Starch can be separated into two principal polysaccharides: amylose and amylopectin. Although the starch from each plant is unique, most starches contain 20 to 25% amylose and 75 to 80% amylopectin.

Complete hydrolysis of both amylose and amylopectin yields only D-glucose. Amylose is composed of continuous, unbranched chains of as many as 4,000 D-glucose units, joined by α-1,4-glycosidic bonds. Amylopectin contains chains up to 10,000 D-glucose units, also joined by α-1,4-glycosidic bonds. In addition, there is considerable branching from this linear network. At branch points, new chains of 24 to 30 units start by α-1,6-glycosidic bonds (Figure 17.4).

Gayvoronskaya_Yana/Shutterstock

Corn starch consists of polysaccharides derived from the endosperm of corn kernels.

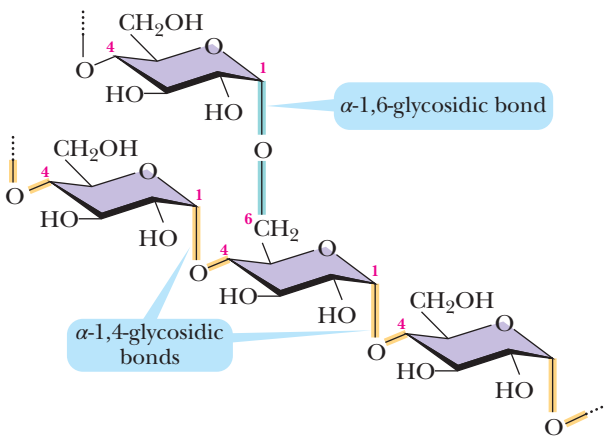


FIGURE 17.4 Amylopectin is a highly branched polymer of D-glucose. Chains consist of 24 to 30 units of D-glucose, joined by α-1,4-glycosidic bonds, and branches created by α-1,6-glycosidic bonds.

Why are carbohydrates stored in plants as polysaccharides rather than monosaccharides, a more directly usable source of energy? The answer has to do with **osmotic pressure**, which is proportional to the molar *concentration*, not the molecular weight, of a solute. If 1,000 molecules of glucose are assembled into one starch macromolecule, a solution containing 1 g of starch per 10 mL will have only 1 one-thousandth the osmotic pressure relative to a solution of 1 g of glucose in the same volume. This feat of packaging is a tremendous advantage because it reduces the strain on various membranes enclosing solutions of such macromolecules.

B. Glycogen

Glycogen is the reserve carbohydrate for animals. Like amylopectin, glycogen is a branched polymer of D-glucose containing approximately 10^6 glucose units, joined by α-1,4- and α-1,6-glycosidic bonds. The total amount of glycogen in the body of a well-nourished adult human being is about 350 g, divided almost equally between liver and muscle.

Moises Fernandez Acosta/Shutterstock.com

Cotton is almost 100% cellulose, a polymer of D-glocose.

C. Cellulose

Cellulose, the most widely distributed plant skeletal polysaccharide, constitutes almost half of the cell-wall material of wood. Cotton is almost pure cellulose.

Cellulose, a linear polymer of D-glucose units joined by β-1,4-glycosidic bonds (Figure 17.5), has an average molar mass of 400,000 g/mol, corresponding to approximately 2,800 glucose units per molecule.

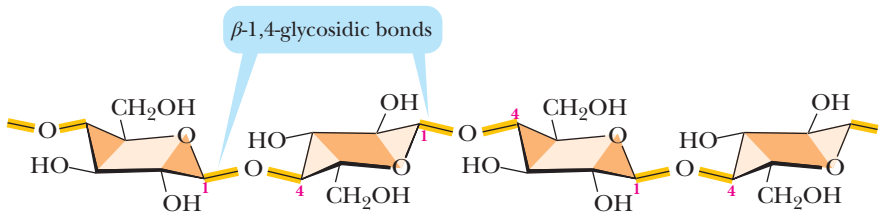


FIGURE 17.5 Cellulose is a linear polymer of D-glucose, joined by β-1,4-glycosidic bonds.

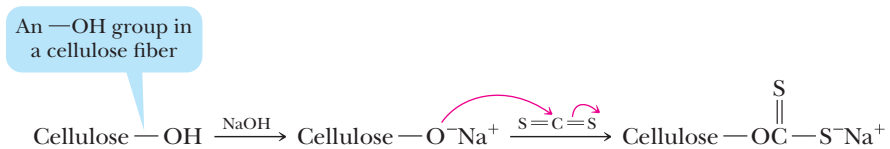
Cellulose molecules act much like stiff rods, a feature that enables them to align themselves side by side into well-organized, water-insoluble fibers in which the OH groups form numerous intermolecular hydrogen bonds. This arrangement of parallel chains in bundles gives cellulose fibers their high mechanical strength and explains why cellulose is insoluble in water. When a piece of cellulose-containing material is placed in water, there are not enough —OH groups on the surface of the fiber to pull individual cellulose molecules away from the strongly hydrogen-bonded fiber.

Humans and other animals cannot use cellulose as food, because our digestive systems do not contain β-glucosidases, enzymes that catalyze the hydrolysis of β-glucosidic bonds. Instead, we have only α-glucosidases; hence, the polysaccharides we use as sources of glucose are starch and glycogen. By contrast, many bacteria and microorganisms do contain β-glucosidases and can digest cellulose. Termites are fortunate (much to our regret) to have such bacteria in their intestines and can use wood as their principal food. Ruminants (cud-chewing animals) and horses can also digest grasses and hay because β-glucosidase-containing microorganisms are present within their alimentary systems.

Acetate rayon, or simply "acetate," is often used as an inexpensive substitute for silk.

D. Textile Fibers from Cellulose

Both **rayon** and acetate rayon are made from chemically modified cellulose and were the first commercially important synthetic textile fibers. In the production of rayon, cellulose fibers are treated with carbon disulfide, CS_2, in aqueous sodium hydroxide. In this reaction, some of the —OH groups on a cellulose fiber are converted to the sodium salt of a xanthate ester, which causes the fibers to dissolve in alkali as a viscous colloidal dispersion:

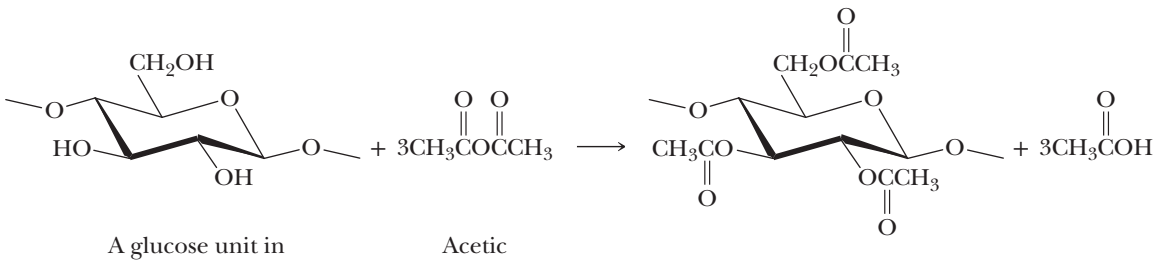


Cellulose (insoluble in water)

Sodium salt of a xanthate ester (a viscous colloidal suspension)

The solution of cellulose xanthate is separated from the alkali-insoluble parts of wood and then forced through a spinneret (a metal disc with many tiny holes) into dilute sulfuric acid to hydrolyze the xanthate ester groups and precipitate regenerated cellulose. Regenerated cellulose extruded as a filament is called viscose rayon thread.

In the industrial synthesis of **acetate rayon**, cellulose is treated with acetic anhydride (Section 14.4B):



A glucose unit in a cellulose fiber — Acetic anhydride — A fully acetylated glucose unit

Acetylated cellulose is then dissolved in a suitable solvent, precipitated, and drawn into fibers known as acetate rayon. The fibers are smooth, soft, resistant to static cling, and dry quickly. One of acetate rayon's most valuable properties is its ability to behave as a thermoplastic (Section 16.1). This allows clothing made from acetate rayon to be heated and permanently pleated upon cooling.

SUMMARY OF KEY QUESTIONS

17.1 What Are Carbohydrates?

Carbohydrates are

- the most abundant organic compounds in the plant world.
- storage forms of chemical energy (glucose, starch, glycogen).
- components of supportive structures in plants (cellulose), crustacean shells (chitin), and connective tissues in animals (acidic polysaccharides).
- essential components of nucleic acids (D-ribose and 2-deoxy-D-ribose).

17.2 What Are Monosaccharides?

- **Monosaccharides** are polyhydroxyaldehydes or polyhydroxyketones or compounds that yield them after hydrolysis.
- The most common monosaccharides have the general formula $C_nH_{2n}O_n$ where n varies from three to nine.
- Their names contain the suffix *-ose*.
- The prefixes *tri-*, *tetr-*, *pent-*, and so on show the number of carbon atoms in the chain.
- The prefix *aldo-* shows an aldehyde, the prefix *keto-* a ketone.
- In a **Fischer projection** of a monosaccharide, the carbon chain is written vertically, with the most highly oxidized carbon toward the top. Horizontal lines show groups projecting above the plane of the page and vertical lines show groups projecting behind the plane of the page.
- A monosaccharide that has the same configuration at its penultimate carbon as D-glyceraldehyde is called a **D-monosaccharide**; one that has the same configuration at its penultimate carbon as L-glyceraldehyde is called an **L-monosaccharide**.
- An amino sugar contains an —NH_2 group in place of an —OH group.

17.3 What Are the Cyclic Structures of Monosaccharides?

- Monosaccharides exist primarily as cyclic hemiacetals.
- The new stereocenter resulting from cyclic hemiacetal formation is referred to as an **anomeric carbon**. The stereoisomers thus formed are called **anomers**.
- A six-membered cyclic hemiacetal form of a monosaccharide is called a **pyranose**; a five-membered cyclic hemiacetal form is called a **furanose**.
- Furanoses and pyranoses can be drawn as **Haworth projections**.
- Pyranoses can be drawn as Haworth projections or as strain-free **chair conformations**.
- The symbol β- indicates that the —OH on the anomeric carbon is on the same side of the ring as the terminal —CH_2OH.
- The symbol α- indicates that —OH on the anomeric carbon is on the opposite side of the ring from the terminal —CH_2OH.
- **Mutarotation** is the change in specific rotation that accompanies the formation of an equilibrium mixture of α- and β-anomers in aqueous solution.

17.4 What Are the Characteristic Reactions of Monosaccharides?

- A **glycoside** is a cyclic acetal derived from a monosaccharide.
- The name of the glycoside is composed of the name of the alkyl or aryl group bonded to the acetal oxygen atom followed by the name of the parent monosaccharide in which the terminal *-e* has been replaced by *-ide*.
- An **alditol** is a polyhydroxy compound formed by reduction of the carbonyl group of a monosaccharide to a hydroxyl group.
- An **aldonic acid** is a carboxylic acid formed by oxidation of the aldehyde group of an aldose.
- Any carbohydrate that reduces an oxidizing agent is called a **reducing sugar**.
- Enzyme-catalyzed oxidation of the terminal $-CH_2OH$ group of a monosaccharide to a COOH group gives a **uronic acid**.

17.5 What Are Disaccharides and Oligosaccharides?

- A **disaccharide** contains two monosaccharide units joined by a **glycosidic bond**.
- Terms applied to carbohydrates containing larger numbers of monosaccharides are **trisaccharide**, **tetrasaccharide**, etc.
- An **oligosaccharide** is a carbohydrate that contains from six to ten monosaccharide units.
- **Sucrose** is a disaccharide consisting of D-glucose joined to D-fructose by an α-1,2-glycosidic bond.
- **Lactose** is a disaccharide consisting of D-galactose joined to D-glucose by a β-1,4-glycosidic bond.
- **Maltose** is a disaccharide of two molecules of D-glucose joined by an α-1,4-glycosidic bond.

17.6 What Are Polysaccharides?

- **Polysaccharides** consist of a large number of monosaccharide units bonded together by glycosidic bonds.
- **Starch** can be separated into two fractions given the names amylose and amylopectin. **Amylose** is a linear polymer of up to 4,000 units of D-glucopyranose joined by α-1,4-glycosidic bonds. **Amylopectin** is a highly branched polymer of D-glucose joined by α-1,4-glycosidic bonds and, at branch points, by α-1,6-glycosidic bonds.
- **Glycogen**, the reserve carbohydrate of animals, is a highly branched polymer of D-glucopyranose joined by α-1,4-glycosidic bonds and, at branch points, by α-1,6-glycosidic bonds.
- **Cellulose**, the skeletal polysaccharide of plants, is a linear polymer of D-glucopyranose joined by β-1,4-glycosidic bonds.
- **Rayon** is made from chemically modified and regenerated cellulose.
- **Acetate rayon** is made by the acetylation of cellulose.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. An acetal of the pyranose or furanose form of a sugar is referred to as a glycoside. (17.4)
2. A monosaccharide can contain the carbonyl of a ketone or the carbonyl of an aldehyde. (17.2)
3. Starch, glycogen, and cellulose are all examples of oligosaccharides. (17.6)
4. An L-sugar and a D-sugar of the same name are enantiomers. (17.2)
5. Alditols are oxidized carbohydrates. (17.4)
6. D-Glucose and D-ribose are diastereomers. (17.2)
7. A pyranoside contains a five-membered ring. (17.3)
8. All monosaccharides dissolve in ether. (17.2)
9. Monosaccharides exist mostly as cyclic hemiacetals. (17.3)
10. A polysaccharide is a glycoside of two monosaccharides. (17.5)
11. α and β in a monosaccharide are used to refer to the positions 1 and 2 carbons away from the carbonyl group. (17.3)
12. Carbohydrates must have the formula $C_n(H_2O)_n$. (17.1)
13. Mutarotation is the establishment of an equilibrium concentration of α and β anomers of a carbohydrate. (17.3)
14. D-Glucose and D-galactose are diastereomers. (17.2)
15. Only acyclic carbohydrates that contain aldehyde groups can act as reducing sugars. (17.4)
16. A methyl glycoside of a monosaccharide cannot act as a reducing sugar. (17.4)
17. The penultimate carbon of an acyclic monosaccharide becomes the anomeric carbon in the cyclic hemiacetal form of the molecule. (17.3)
18. A Fischer projection may be rotated 90°. (17.2)

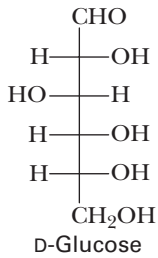
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) T (2) T (3) F (4) T (5) F (6) F (7) F (8) F (9) T (10) F (11) F (12) F (13) T (14) T (15) F (16) T (17) F (18) F

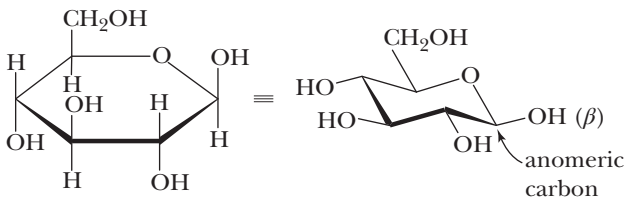
KEY REACTIONS

1. Formation of Cyclic Hemiacetals (Section 17.3)

A monosaccharide existing as a five-membered ring is a furanose; one existing as a six-membered ring is a pyranose. A pyranose is most commonly drawn as a Haworth projection or a chair conformation:



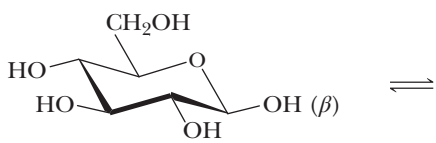
D-Glucose



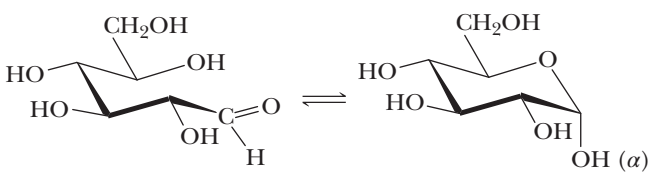
β-D-Glucopyranose
(β-D-Glucose)

2. Mutarotation (Section 17.3C)

Anomeric forms of a monosaccharide are in equilibrium in aqueous solution. Mutarotation is the change in specific rotation that accompanies this equilibration:



β-D-Glucopyranose
$[\alpha]_D^{25}$ + 18.7°

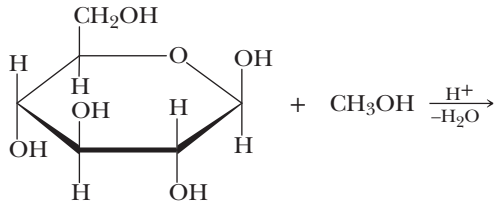


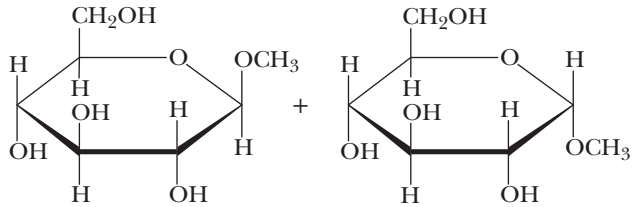
Open-chain form

α-D-Glucopyranose
$[\alpha]_D^{25}$ + 112°

3. Formation of Glycosides (Section 17.4A)

Treatment of a monosaccharide with an alcohol in the presence of an acid catalyst forms a cyclic acetal called a glycoside:

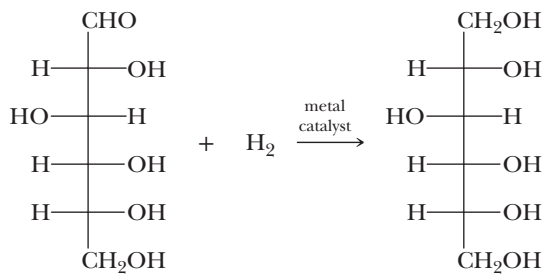




The bond to the new —OR group is called a glycosidic bond.

4. Reduction to Alditols (Section 17.4B)

Reduction of the carbonyl group of an aldose or a ketose to a hydroxyl group yields a polyhydroxy compound called an alditol:

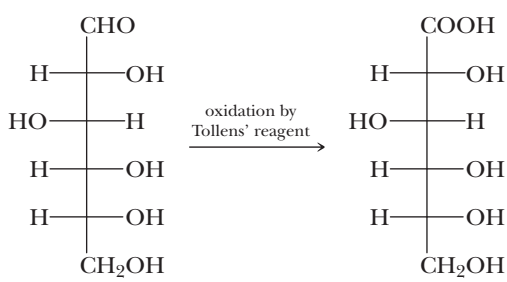


D-Glucose

D-Glucitol
(D-Sorbitol)

5. Oxidation to an Aldonic Acid (Section 17.4C)

Oxidation of the aldehyde group of an aldose to a carboxyl group by a mild oxidizing agent gives a polyhydroxycarboxylic acid called an aldonic acid:



D-Glucose

D-Gluconic acid

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 17.2 Monosaccharides

17.8 What is the difference in structure between an aldose and a ketose? Between an aldopentose and a ketopentose?

17.9 Which hexose is also known as dextrose?

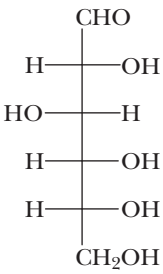
17.10 What does it mean to say that D- and L-glyceraldehydes are enantiomers?

17.11 Explain the meaning of the designations D and L as used to specify the configuration of carbohydrates.

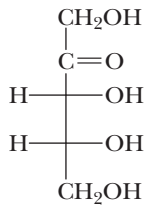
17.12 How many stereocenters are present in D-glucose? In D-ribose? How many stereoisomers are possible for each monosaccharide?

17.13 Which compounds are D-monosaccharides and which are L-monosaccharides? **(See Example 17.1)**

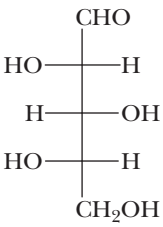
(a)



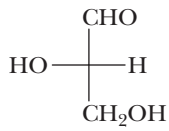
(c)



(b)



(d)



17.14 Draw Fischer projections for L-ribose and L-arabinose. **(See Example 17.1)**

17.15 Explain why all mono- and disaccharides are soluble in water.

© Yixin Chen/iStockphoto

The foxglove plant produces the important cardiac medication digitalis.

17.16 What is an amino sugar? Name the three amino sugars most commonly found in nature.

***17.17** 2,6-Dideoxy-D-altrose, known alternatively as D-digitoxose, is a monosaccharide obtained from the hydrolysis of digitoxin, a natural product extracted from purple foxglove *(Digitalis purpurea)*. Digitoxin has found wide use in cardiology because it reduces the pulse rate, regularizes heart rhythm, and strengthens the heartbeat. Draw the structural formula of 2,6-dideoxy-D-altrose.

SECTION 17.3 The Cyclic Structure of Monosaccharides

17.18 Define the term *anomeric carbon*.

17.19 Explain the conventions for using α and β to designate the configurations of cyclic forms of monosaccharides.

17.20 Are α-D-glucose and β-D-glucose anomers? Explain. Are they enantiomers? Explain.

17.21 Are α-D-gulose and α-L-gulose anomers? Explain.

17.22 In what way are chair conformations a more accurate representation of molecular shape of hexopyranoses than are Haworth projections?

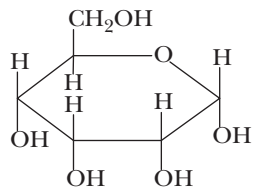
17.23 Draw α-D-glucopyranose (α-D-glucose) as a Haworth projection. Now, using only the following information, draw Haworth projections for these monosaccharides: **(See Example 17.2)**

(a) α-D-Mannopyranose (α-D-mannose). The configuration of D-mannose differs from that of D-glucose only at carbon 2.

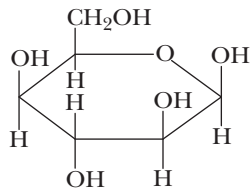
(b) α-D-Gulopyranose (α-D-gulose). The configuration of D-gulose differs from that of D-glucose at carbons 3 and 4.

17.24 Convert each Haworth projection to an open-chain form and then to a Fischer projection:

(a)



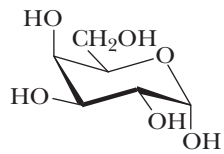
(b)



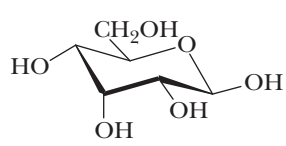
Name the monosaccharides you have drawn.

17.25 Convert each chair conformation to an open-chain form and then to a Fischer projection:

(a)



(b)



Name the monosaccharides you have drawn.

17.26 The configuration of D-arabinose differs from the configuration of D-ribose only at carbon 2. Using this information, draw a Haworth projection for α-D-arabinofuranose (α-D-arabinose). **(See Examples 17.2, 17.3)**

17.27 Explain the phenomenon of mutarotation with reference to carbohydrates. By what means is mutarotation detected?

17.28 The specific rotation of α-D-glucose is +112.2°. What is the specific rotation of α-L-glucose?

17.29 When α-D-glucose is dissolved in water, the specific rotation of the solution changes from +112.2° to +52.7°. Does the specific rotation of α-L-glucose also change when it is dissolved in water? If so, to what value does it change?

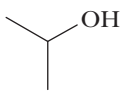
SECTION 17.4 Reactions of Monosaccharides

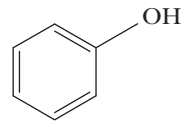
17.30 Draw the structural formula for ethyl α-D-galactopyranoside (ethyl α-D-galactoside). Label the anomeric carbon and the glycosidic bond. **(See Example 17.4)**

17.31 Draw the structural formula for methyl β-D-mannopyranoside (methyl β-D-mannoside). Label the anomeric carbon and the glycosidic bond. **(See Example 17.4)**

17.32 Show the two possible products of each reaction (refer to Table 17.1). Label the α and β anomers in each reaction. **(See Example 17.4)**

(a) D-Gulose + CH_3CH_2OH $\xrightarrow{\text{dilute } H_2SO_4}$

(b) D-Altrose +  $\xrightarrow{\text{dilute } H_2SO_4}$

(c) D-Xylos +  $\xrightarrow{\text{dilute } H_2SO_4}$

17.33 Draw a structural formula for the β-*N*-glycoside formed between (a) D-ribofuranose and thymine and (b) D-ribofuranose and guanine. Label the anomeric carbon and the *N*-glycosidic bond. **(See Example 17.5)**

17.34 Draw Fischer projections for the product(s) formed by the reaction of D-galactose with the following compounds, and state whether each product is optically active or optically inactive: **(See Example 17.6)**

(a) $NaBH_4$ in H_2O (b) $AgNO_3$ in NH_3, H_2O

17.35 Repeat Problem 17.34, but using D-ribose in place of D-galactose. **(See Example 17.6)**

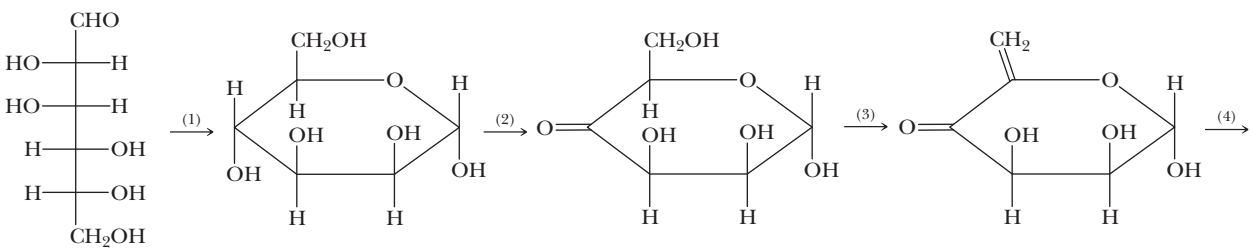
17.36 The reduction of D-fructose by $NaBH_4$ gives two alditols, one of which is D-sorbitol. Name and draw a structural formula for the other alditol. **(See Example 17.6)**

17.37 There are four D-aldopentoses (Table 17.1). If each is reduced with $NaBH_4$, which yield optically active alditols? Which yield optically inactive alditols? **(See Example 17.6)**

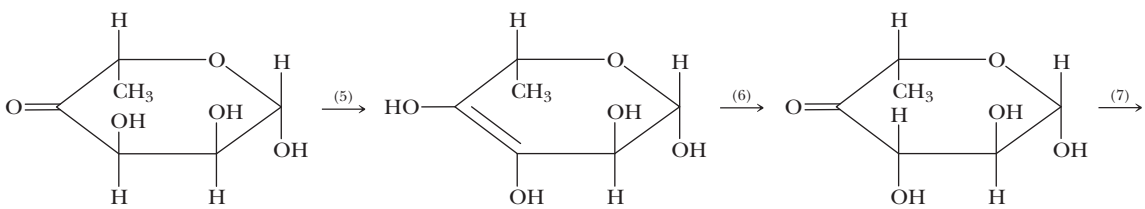
17.38 Account for the observation that the reduction of D-glucose with $NaBH_4$ gives an optically active alditol, whereas the reduction of D-galactose with $NaBH_4$ gives an optically inactive alditol. **(See Example 17.6)**

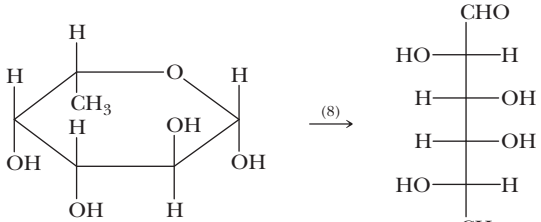
17.39 Which two D-aldohexoses give optically inactive (meso) alditols on reduction with $NaBH_4$? **(See Example 17.6)**

***17.40** L-Fucose, one of several monosaccharides commonly found in the surface polysaccharides of animal cells (Chemical Connections 17B), is synthesized biochemically from D-mannose in the following eight steps:



D-Mannose





L-Fucose

(a) Describe the type of reaction (oxidation, reduction, hydration, dehydration, or the like) involved in each step.

(b) Explain why this monosaccharide, which is derived from D-mannose, now belongs to the L series.

SECTION 17.5 Disaccharides and Oligosaccharides

17.41 Define the term *glycosidic bond*.

17.42 What is the difference in meaning between the terms *glycosidic bond* and *glucosidic bond*?

17.43 Do glycosides undergo mutarotation?

***17.44** In making candy or syrups from sugar, sucrose is boiled in water with a little acid, such as lemon juice. Why does the product mixture taste sweeter than the starting sucrose solution?

17.45 Which disaccharides are reduced by $NaBH_4$?

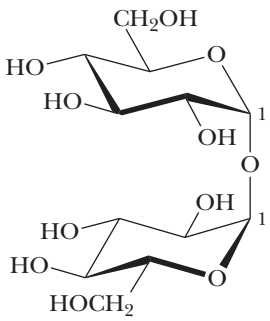
(a) Sucrose

(b) Lactose

(c) Maltose

17.46 Draw Haworth and chair formulas for the β form of a disaccharide in which two units of D-glucopyranose are joined by a β-1,4-glycosidic bond. **(See Example 17.7)**

***17.47** Trehalose is found in young mushrooms and is the chief carbohydrate in the blood of certain insects. Trehalose is a disaccharide consisting of two D-monosaccharide units, each joined to the other by an α-1,1-glycosidic bond:



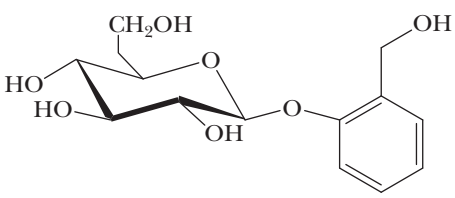
Trehalose

(a) Is trehalose a reducing sugar?

(b) Does trehalose undergo mutarotation?

(c) Name the two monosaccharide units of which trehalose is composed.

***17.48** Hot-water extracts of ground willow bark are an effective pain reliever. Unfortunately, the liquid is so bitter that most persons refuse it. The pain reliever in these infusions is salicin:



Salicin

Name the monosaccharide unit in salicin.

SECTION 17.6 Polysaccharides

17.49 What is the difference in structure between oligosaccharides and polysaccharides?

17.50 Name three polysaccharides that are composed of units of D-glucose. In which of the three polysaccharides are the glucose units joined by α-glycosidic bonds? In which are they joined by β-glycosidic bonds?

17.51 Starch can be separated into two principal polysaccharides: amylose and amylopectin. What is the major difference in structure between the two?

***17.52** A Fischer projection of *N*-acetyl-D-glucosamine is given in Section 17.2E.

(a) Draw Haworth and chair structures for the α- and β-pyranose forms of this monosaccharide.

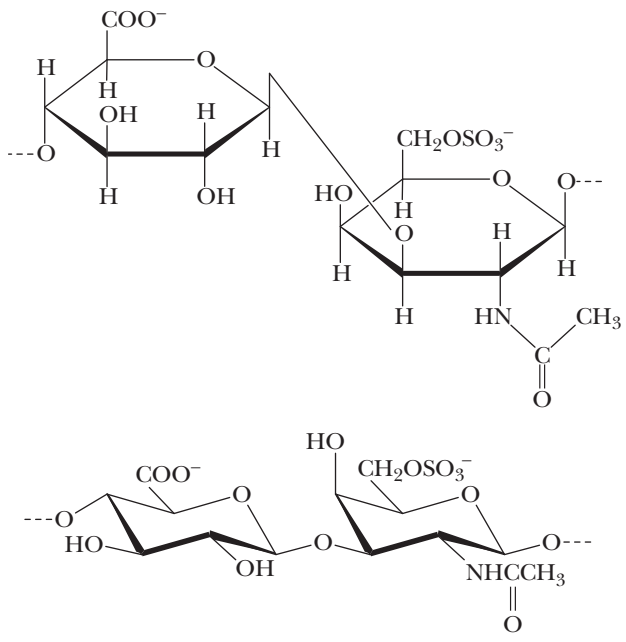
(b) Draw Haworth and chair structures for the disaccharide formed by joining two units of the pyranose form of *N*-acetyl-D-glucosamine by a β-1,4-glucosidic bond. If your drawing is correct, you have the structural formula for the repeating dimer of chitin, the structural polysaccharide component of the shell of lobsters and other crustaceans.

***17.53** Propose structural formulas for the repeating disaccharide unit in these polysaccharides (see Section 17.4D for treatment of uronic acids):

(a) Alginic acid, isolated from seaweed, is used as a thickening agent in ice cream and other foods. Alginic acid is a polymer of D-mannuronic acid in the pyranose form, joined by β-1,4-glycosidic bonds.

(b) Pectic acid is the main component of pectin, which is responsible for the formation of jellies from fruits and berries. Pectic acid is a polymer of D-galacturonic acid in the pyranose form joined by α-1,4-glycosidic bonds.

***17.54** The first formula is a Haworth projection, and the second is a chair conformation for the repeating disaccharide unit in chondroitin 6-sulfate:



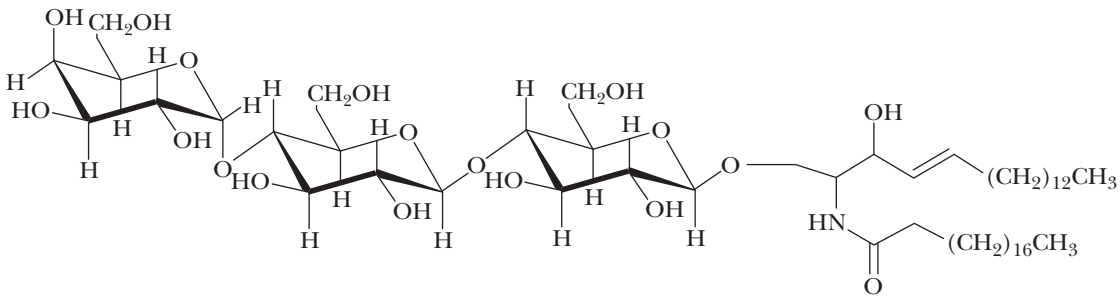
This biopolymer acts as a flexible connecting matrix between the tough protein filaments in cartilage and is available as a dietary supplement, often combined with D-glucosamine sulfate. Some believe that the combination can strengthen and improve joint flexibility.

(a) From what two monosaccharide units is the repeating disaccharide unit of chondroitin 6-sulfate derived?

(b) Describe the glycosidic bond between the two units.

***17.55** Certain complex lipids are constantly being synthesized and decomposed in the body. In several genetic diseases classified as lipid storage diseases, some of the enzymes needed to decompose the complex lipid are defective or missing. As a consequence, the complex lipids accumulate and cause enlarged liver and spleen, mental retardation, blindness, and in certain cases early death. At present no treatment is available for these diseases. The best way to prevent them is genetic counseling. Some of them can be diagnosed during fetal development.

The following is the structure of the lipid that accumulates in Fabray's disease. The genetic defect in this case is that the enzyme α-galactosidase is either missing or defective. This enzyme catalyzes the hydrolysis of the glycosidic bonds formed by α-D-galactopyranose.



(c) Name the three hexoses present in this lipid.

(d) Describe the glycosidic bond between each.

(e) Would you expect this molecule to be soluble or insoluble in water? Explain.

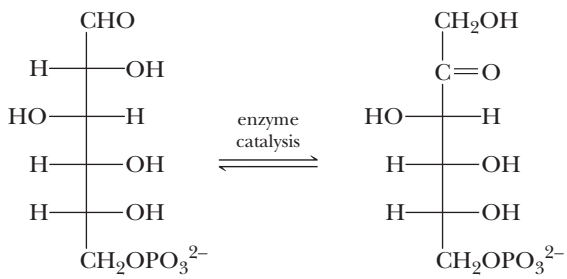
LOOKING AHEAD

***17.56** One step in glycolysis, the pathway that converts glucose to pyruvate (Section 21.3), involves an enzyme-catalyzed conversion of dihydroxyacetone phosphate to D-glyceraldehyde 3-phosphate:

Dihydroxyacetone phosphate — D-Glyceraldehyde 3-phosphate

Show that this transformation can be regarded as two enzyme-catalyzed keto–enol tautomerizations (Section 12.8).

***17.57** One pathway for the metabolism of glucose 6-phosphate is its enzyme-catalyzed conversion to fructose 6-phosphate:



D-Glucose 6-phosphate — D-Fructose 6-phosphate

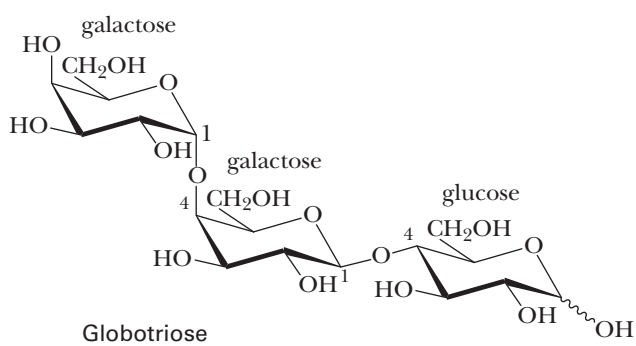
Show that this transformation can be regarded as two enzyme-catalyzed keto–enol tautomerizations.

17.58 Epimers are carbohydrates that differ in configuration at only one stereocenter.

(a) Which of the aldohexoses are epimers of each other?

(b) Are all anomer pairs also epimers of each other? Explain. Are all epimers also anomers? Explain.

***17.59** Oligosaccharides are very valuable therapeutically and are especially difficult to synthesize, even though the starting materials are readily available. Shown is the structure of globotriose, the receptor for a series of toxins synthesized by some strains of *E. coli*:



Globotriose

From left to right, globotriose consists of an α-1,4-linkage of galactose to galactose that is part of a β-1,4-linkage to glucose. The squiggly line indicates that the configuration at that carbon can be α or β. Suggest why it would be difficult to synthesize this trisaccharide, for example, by first forming the galactose–galactose glycosidic bond and then forming the glycosidic bond to glucose.

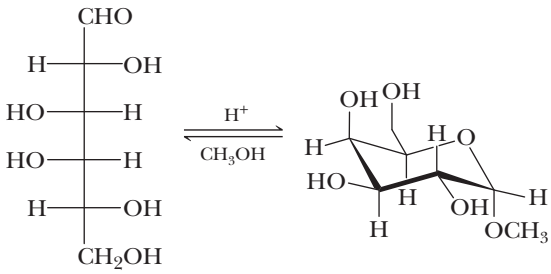
GROUP LEARNING ACTIVITIES

17.60 Pair up with another student. Each of you should select an aldohexose (refer to Table 17.1 for some possibilities). Decide whether the two carbohydrates you selected are:

(a) epimers
(b) enantiomers
(c) diasteromers
(d) D/L isomers

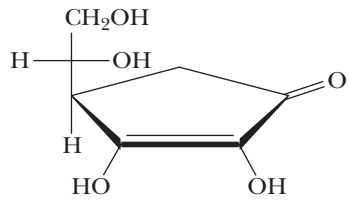
17.61 Discuss how nature settled upon the D form of carbohydrates as the sole stereoisomeric form in living systems. Use the Internet to learn about different scientific theories applicable to this question and debate the merits of each.

17.62 Work as a group to provide the mechanism for the reaction shown below.



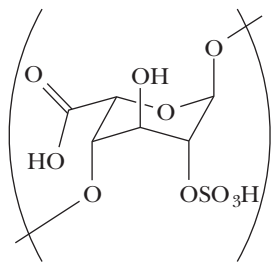
Hint: Each step is a mechanistic pattern we have covered in this or previous chapters.

17.63 The structural formula of L-ascorbic acid (vitamin C) resembles that of a monosaccharide. Humans do not have the enzyme systems required for the synthesis of L-ascorbic acid; therefore, for us, it is a vitamin. Approximately 66 million kilograms of vitamin C are synthesized every year in the United States. Ascorbic acid contains four hydroxyl groups. With your group, determine which —OH group is most acidic and debate the merits of your selection. Recall from Section 2.5 that various structural features can enhance the stability of a conjugate base, thus increasing the acidity of the original acid.



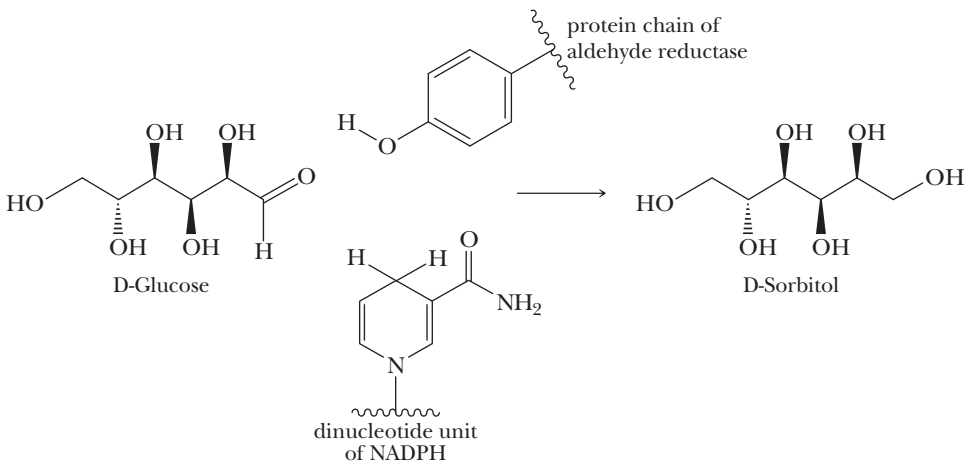
L-Ascorbic acid
(Vitamin C)

17.64 Heparin is an anticoagulant that is a polysaccharide of varying chain size. One of its monomer units is shown below. Classify this saccharide-based unit. From which hexose is this unit derived? Discuss the form this monomer unit would assume at biological pH (7.0—7.2).



Monomer unit of heparin

17.65 In Section 17.4B, we learned that glucose is reduced to sorbitol when treated with $NaBH_4$. The biological analog of this reaction involves the NADPH-mediated reduction of glucose in the active site of the enzyme aldehyde reductase. This reaction is prevalent in patients with diabetes, because the normal mechanism of metabolizing glucose is unavailable to those who cannot regulate insulin. Propose a mechanism for this reaction, keeping in mind that nature is so efficient that both the reduction of the carbonyl and the generation of the —OH group occur simultaneously. As a group, discuss how nature is often a much better synthetic chemist than synthetic chemists!

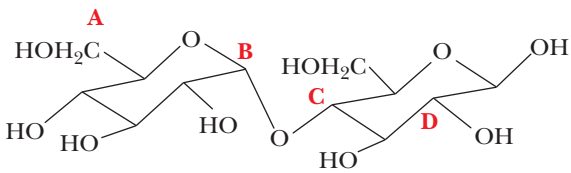


PUTTING IT TOGETHER

The following problems bring together concepts and material from Chapters 15–17. Although the focus may be on these chapters, the problems will also build upon concepts discussed throughout the text thus far.

Choose the best answer for each of the following questions.

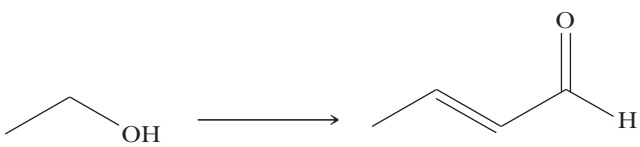
1. Which carbon on β-maltose will be oxidized by Tollens' reagent?



β-Maltose

(a) **A** (b) **B** (c) **C**
(d) **D** (e) **none of the above**

2. What sequence of reagents will accomplish the following transformation?



(a) 1) PCC/CH_2Cl_2
2) $NaOH/H_2O$
3) H^+/H_2O

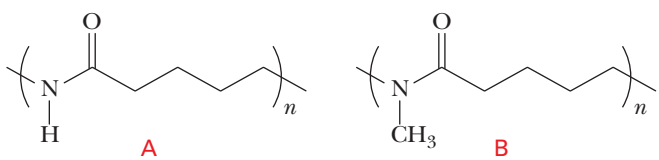
(b) 1) H_2CrO_4/H_2SO_4
2) $NaOH/H_2O$
3) H^+/H_2O

(c) 1) $NaOH/H_2O$
2) H_2CrO_4/H_2SO_4
3) $NaOH/H_2O$
4) H^+/H_2O

(d) 1) $LiAlH_4/Et_2O$
2) H^+/H_2O
3) $NaOH/H_2O$

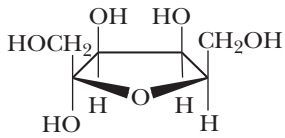
(e) 1) $NaBH_4/EtOH$
2) H^+/H_2O
3) $NaOH/H_2O$

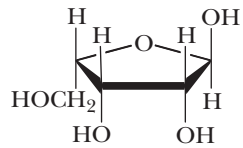
3. Assuming that the following two polymers are manufactured in similar ways, which of the following statements is *true*?

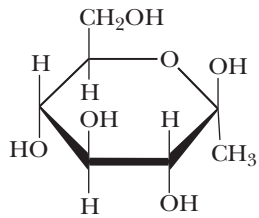


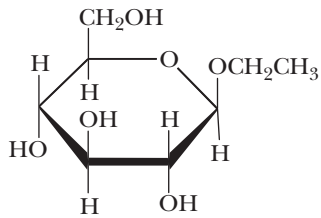
(a) Polymer **A** will be easier to synthesize than polymer **B**.
(b) Polymer **A** will be more amorphous than polymer **B**.
(c) Polymer **A** will be weaker than polymer **B**.
(d) Polymer **A** will have a higher T_g than polymer **B**.
(e) None of the above.

4. Which of the following carbohydrates does *not* undergo mutarotation?

(a) 

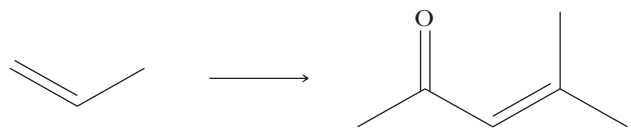
(b) 

(c) 

(d) 

(e) All of these

5. What sequence of reagents will accomplish the following transformation?



(a) $\xrightarrow{HBr} \xrightarrow[H_2SO_4]{H_2CrO_4} \xrightarrow[H_2O]{NaOH}$

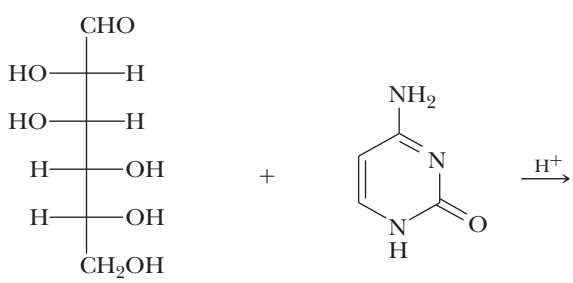
(b) $\xrightarrow[H_2O]{NaOH} \xrightarrow[H_2O]{H^+}$

(c) $\xrightarrow[H_2SO_4]{H_2CrO_4} \xrightarrow[H_2O]{NaOH} \xrightarrow[H_2O]{H^+}$

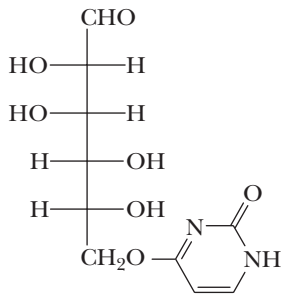
(d) $\xrightarrow[H_2O]{H_2SO_4} \xrightarrow[H_2SO_4]{H_2CrO_4} \xrightarrow[H_2O]{NaOH} \xrightarrow[H_2O]{H^+}$

(e) $\xrightarrow[H_2O]{H_2SO_4} \xrightarrow[Et_2O]{LiAlH_4} \xrightarrow[H_2O]{H^+} \xrightarrow[H_2O]{NaOH} \xrightarrow[H_2O]{H^+}$

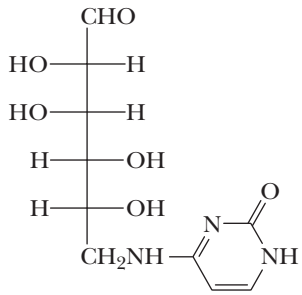
6. Select the most likely product of the following reaction.



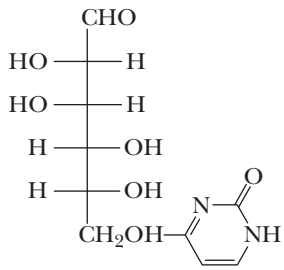
(a)



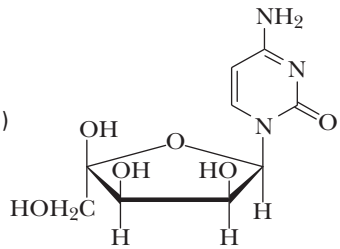
(b)



(c)

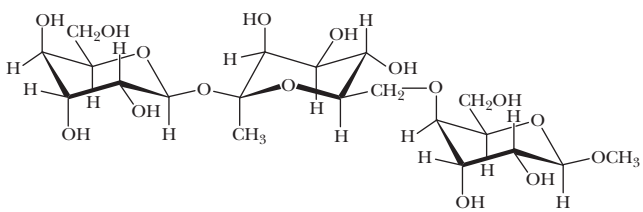


(d)



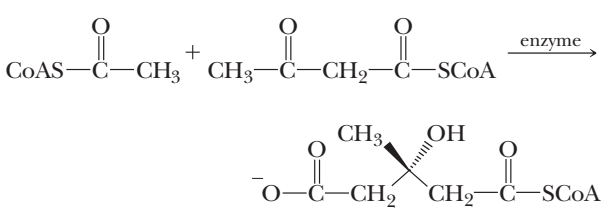
(e) None of the above

7. How many glycosidic bonds exist in the following polysaccharide?



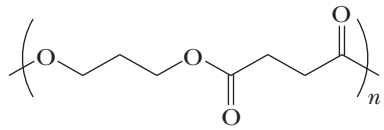
(a) one (b) two (c) three (d) four (e) five

8. Which of the following best classifies the following biological process?

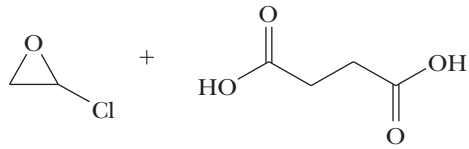


(a) Claisen condensation
(b) Aldol reaction
(c) Nucleophilic acyl substitution
(d) β-elimination
(e) Both **A** and **C**

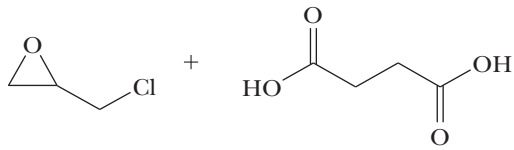
9. Identify the monomer(s) required for the synthesis of the following polymer:



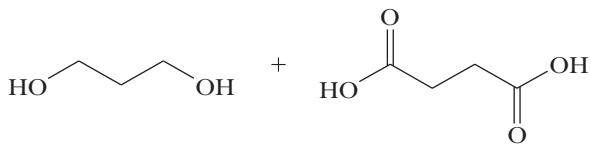
(a)



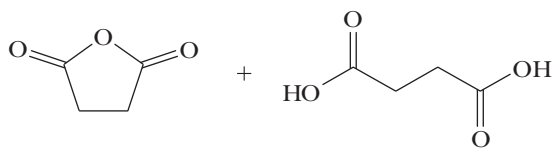
(b)



(c)



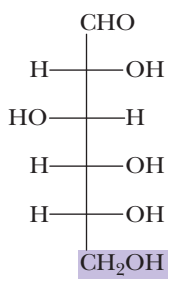
(d)



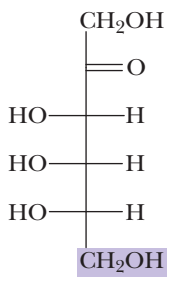
(e) None of these

10. An unknown carbohydrate is placed in a solution of $NaBH_4$/EtOH. After isolating the product, it was discovered that no alditol products were formed. Which of the following carbohydrates could be the unknown?

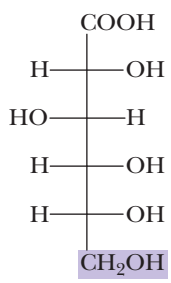
(a)



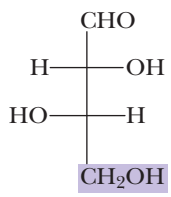
(b)



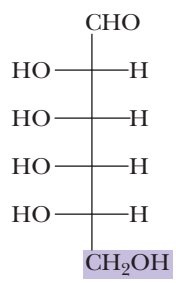
(c)



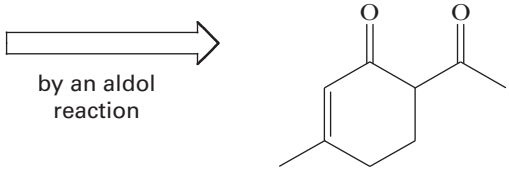
(d)

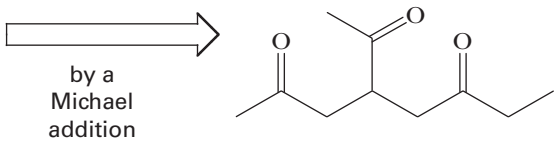


(e)

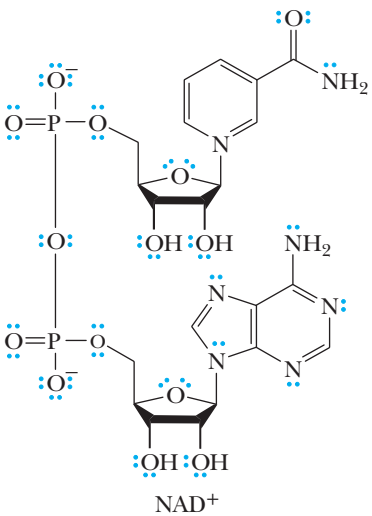


11. Each of the products shown can be made by the reaction indicated under the arrow. Provide a structure for the starting compound(s) needed to produce the product shown. Then show the mechanism of its formation. Show all charges and lone pairs of electrons in your structures.

(a) 

(b) 

12. NAD^+ is a coenzyme found in all living cells. It acts to carry electrons during biological reactions.



(a) Assign the formal charge in NAD^+ to the appropriate atom.

(b) Is NAD^+ a reducing sugar?

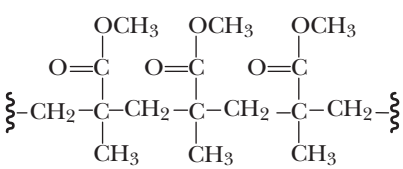
(c) Identify the glycosidic bonds in NAD^+.

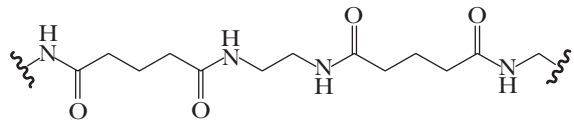
(d) From what naturally occurring sugar(s) is NAD^+ derived?

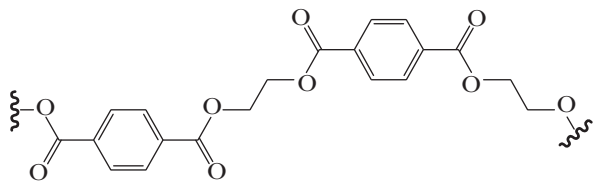
(e) Are the two monosaccharide units α-anomers or β-anomers?

(f) Does NAD^+ undergo mutarotation?

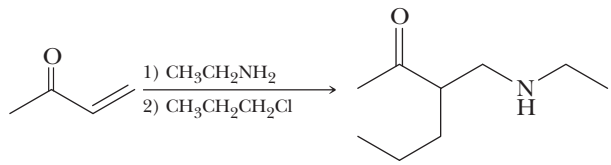
13. Redraw each polymer using the notation in which parentheses are placed around the repeating unit. Identify each as chain-growth or step-growth polymers and identify the monomers required for its synthesis.

(a) 

(b) 

(c) 

14. Provide a mechanism for the following series of reactions. Show all charges and lone pairs of electrons in your structures as well as the structures of all intermediates.

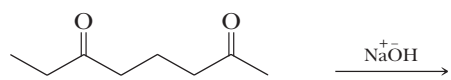


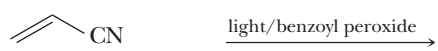
15. Select the polymer from each pair that would have the higher glass transition temperature and provide an explanation for selection.

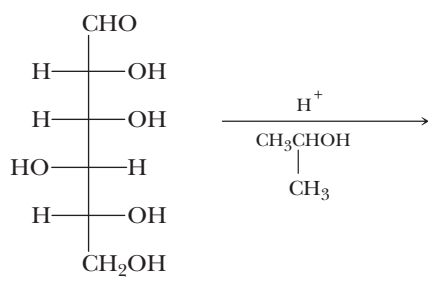
(a) 

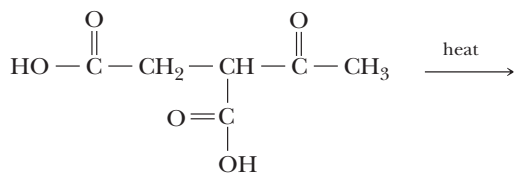
(b) 

16. Predict the major product of each of the following reactions.

(a) 

(b) 

(c) 

(d) 

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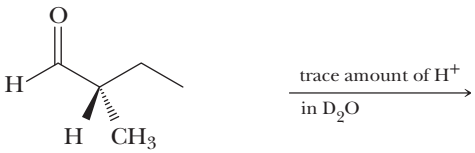

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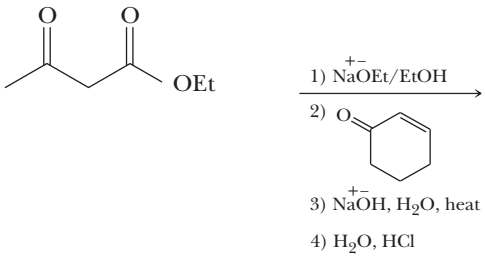
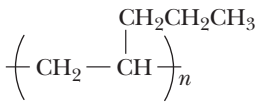
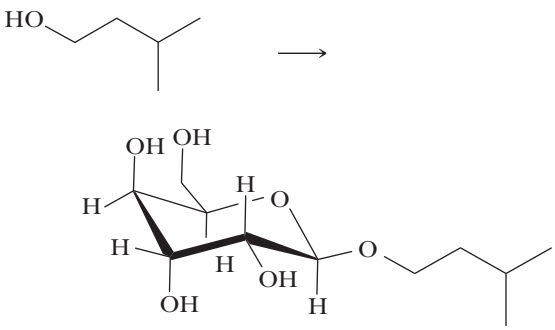


17. Complete the following chemical transformations.

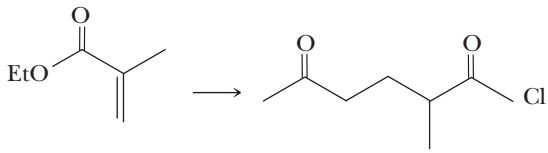
(a) any hydrocarbon ⟶



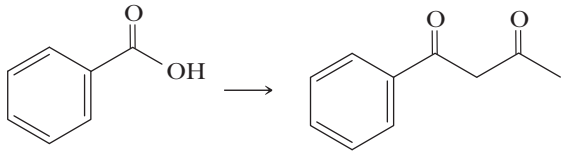
(b)



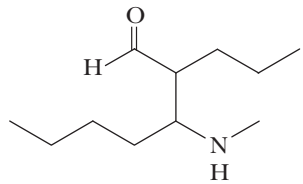
(c)



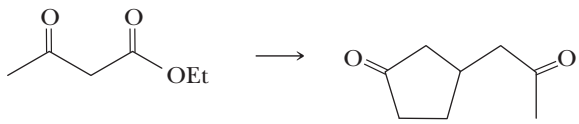
(d)

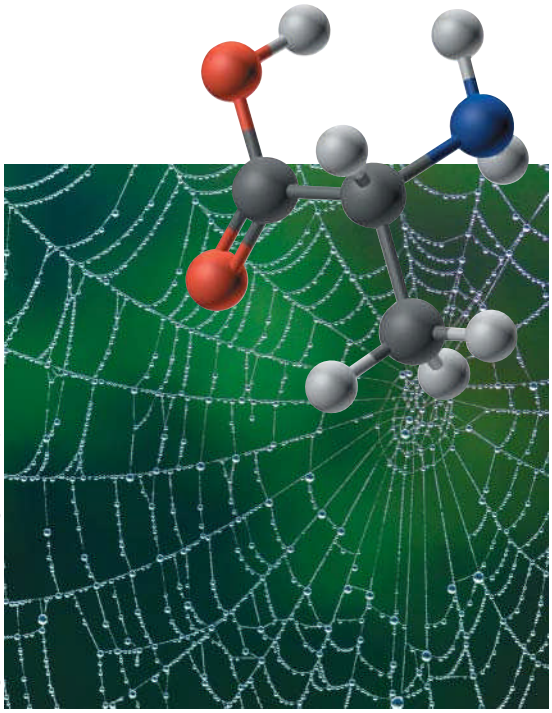


(e) any carbonyl compound of 5 carbons or less ⟶

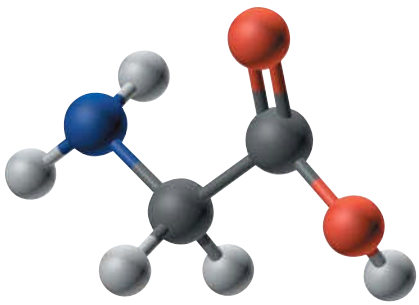


(f)





Amino Acids and Proteins



18

Spider silk is a fibrous protein that exhibits unmatched strength and toughness. Inset: Models of D-alanine and glycine, the major components of the fibrous protein of silk.

KEY QUESTIONS

HOW TO

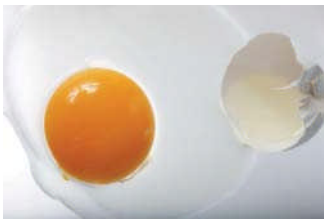
CHEMICAL CONNECTIONS

WE BEGIN THIS CHAPTER with a study of amino acids, the building blocks of the biological macromolecules known as proteins, and compounds whose chemistry is built on two familiar classes of compounds, the amines (Chapter 10) and carboxylic acids (Chapter 13). We will learn that the physical and acid–base properties of amino acids are crucial in determining the structures of proteins, which in turn determine their many functions in living organisms.

18.1 What Are the Many Functions of Proteins?

Proteins are among the most important of all biological compounds. Among the functions performed by these vital molecules are the following:

- *Structure*—Structural proteins such as collagen and keratin are the chief constituents of skin, bones, hair, and nails.
- *Catalysis*—Virtually all reactions that take place in living systems are catalyzed by a special group of proteins called enzymes. Without enzymes, these many reactions would take place so slowly as to be useless.



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Both the egg white and yolk contain large amounts of proteins, each serving a specific biological function.

- *Movement*—Muscle expansion and contraction are involved in every movement we make. Muscle fibers are made of proteins called myosin and actin.
- *Transport*—A large number of proteins perform transport duties. The protein hemoglobin is responsible for the transport of oxygen from the lungs to tissues. Other proteins transport molecules across cell membranes.
- *Hormones*—Many hormones are proteins, including insulin and human growth hormone.
- *Protection*—The production of a group of proteins called antibodies is one of the body's major defenses against disease. The function of the protein fibrinogen is to promote blood clotting.
- *Regulations*—Some proteins not only control the expression of genes, thereby regulating the kind of protein synthesized in a particular cell, but also dictate when such synthesis takes place.

Proteins have other functions as well. Even this brief list, however, should convince you of their vital role in living organisms. A typical cell contains about 9,000 different proteins.

18.2 What Are Amino Acids?

A. Structure

Amino acid A compound that contains both an amino group and a carboxyl group.

α-Amino acid An amino acid in which the amino group is on the carbon adjacent to the carboxyl group.

Zwitterion An internal salt of an amino acid.

An **amino acid** is a compound that contains both a carboxyl group and an amino group. Although many types of amino acids are known, the ***α*-amino acids** are the most significant in the biological world because they are the monomers from which proteins are constructed. A general structural formula of an α-amino acid is shown in Figure 18.1.

Although Figure 18.1(a) is a common way of writing structural formulas for an amino acid, it is not accurate because it shows an acid (—COOH) and a base ($—NH_2$) within the same molecule. These acidic and basic groups react with each other to form an internal salt (a dipolar ion) [Figure 18.1(b)]. This internal salt is given the special name **zwitterion**. Note that a zwitterion has no net charge; it contains one positive charge and one negative charge.

Because they exist as zwitterions, amino acids have many of the properties associated with salts. They are crystalline solids with high melting points and are fairly soluble in water, but insoluble in nonpolar organic solvents such as ether and hydrocarbon solvents.

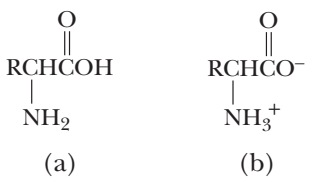


FIGURE 18.1 An α-amino acid. (a) Unionized form and (b) internal salt (zwitterion) form.

B. Chirality

With the exception of glycine, H_2NCH_2COOH, all protein-derived amino acids have at least one stereocenter and therefore are chiral. Figure 18.2 shows Fischer projection formulas for the enantiomers of alanine. The vast majority of carbohydrates in the biological world are of the D-series (Section 17.2), whereas the vast majority of α-amino acids in the biological world are of the L-series.

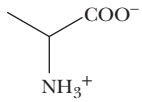
C. Protein-Derived Amino Acids

Table 18.1 gives common names, structural formulas, and standard three-letter and one-letter abbreviations for the 20 common L-amino acids found in proteins. The amino acids shown are divided into four categories: those with nonpolar side chains; those with polar, but un-ionized side chains; those with acidic side chains; and those with basic side chains. As you study the information in this table, note the following points:

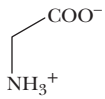
TABLE 18.1 The 20 Common Amino Acids Found in Proteins (*Note:* Each ionizable group is shown in the form present in highest concentration in aqueous solution at pH 7.0.)

Nonpolar Side Chains

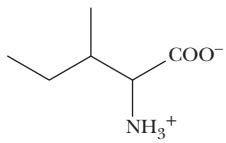
Alanine (Ala, A)



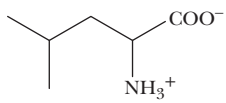
Glycine (Gly, G)



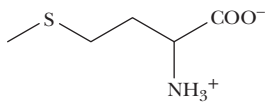
Isoleucine (Ile, I)



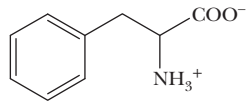
Leucine (Leu, L)



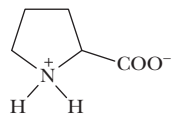
Methionine (Met, M)



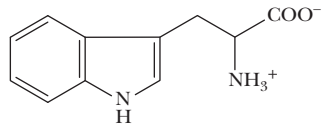
Phenylalanine (Phe, F)



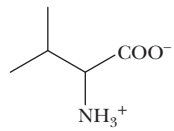
Proline (Pro, P)



Tryptophan (Trp, W)

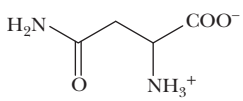


Valine (Val, V)

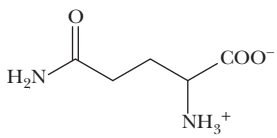


Polar Side Chains

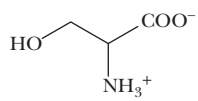
Asparagine (Asn, N)



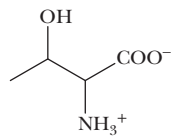
Glutamine (Gln, Q)



Serine (Ser, S)

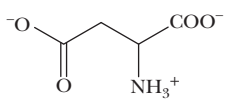


Threonine (Thr, T)

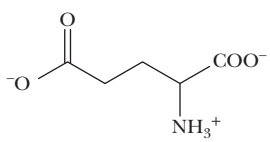


Acidic Side Chains

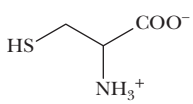
Aspartic acid (Asp, D)



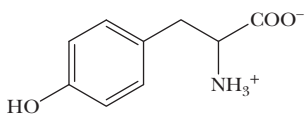
Glutamic acid (Glu, E)



Cysteine (Cys, C)

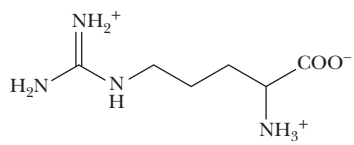


Tyrosine (Tyr, Y)

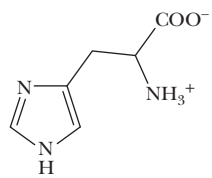


Basic Side Chains

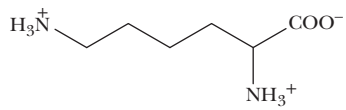
Arginine (Arg, R)

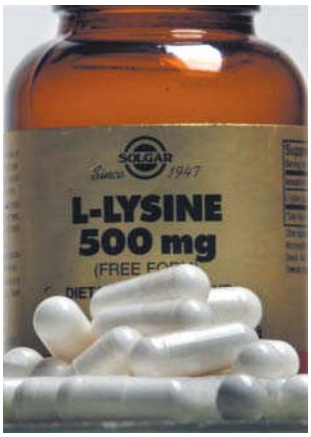


Histidine (His, H)



Lysine (Lys, K)





Lawrence K. Ho/Los Angeles Times via/Getty Images, Inc.

Dietary supplements that supply one or more amino acids abound.

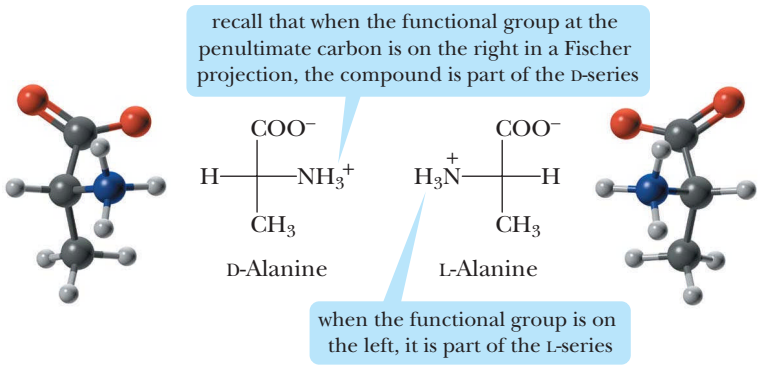


FIGURE 18.2 The enantiomers of alanine. The vast majority of α-amino acids in the biological world have the L-configuration at the α-carbon.

1. All 20 of these protein-derived amino acids are α-amino acids, meaning that the amino group is located on the carbon alpha to the carboxyl group.

2. For 19 of the 20 amino acids, the α-amino group is primary. Proline is different: Its α-amino group is secondary.

3. With the exception of glycine, the α-carbon of each amino acid is a stereocenter. Although not shown in the table, all 19 chiral amino acids have the same relative configuration at the α-carbon. In the D, L convention, all are L-amino acids.

4. Isoleucine and threonine contain a second stereocenter. Four stereoisomers are possible for each amino acid, but only one of the four is found in proteins.

5. The sulfhydryl group of cysteine, the imidazole group of histidine, and the phenolic hydroxyl of tyrosine are partially ionized at pH 7.0, but the ionized form is not the major form present at that pH.

EXAMPLE 18.1

Of the 20 protein-derived amino acids shown in Table 18.1, how many contain (a) aromatic rings, (b) side-chain hydroxyl groups, (c) phenolic —OH groups, and (d) sulfur?

STRATEGY

Study the structural formulas of the amino acids given in Table 18.1.

SOLUTION

(a) Phenylalanine, tryptophan, tyrosine, and histidine contain aromatic rings.

(b) Serine and threonine contain side-chain hydroxyl groups.

(c) Tyrosine contains a phenolic —OH group.

(d) Methionine and cysteine contain sulfur.

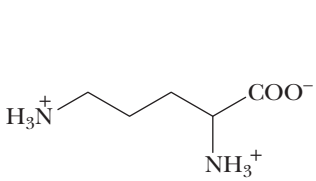
See problems 18.14, 18.15

PROBLEM 18.1

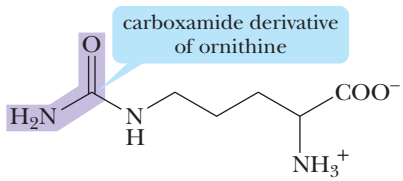
Of the 20 protein-derived amino acids shown in Table 18.1, (a) which contain no stereocenter and (b) which contain two stereocenters?

D. Some Other Common L-Amino Acids

Although the vast majority of plant and animal proteins are constructed from just these 20 α-amino acids, many other amino acids are also found in nature. Ornithine and citrulline, for example, are found predominantly in the liver and are integral parts of the urea cycle, the metabolic pathway that converts ammonia to urea:

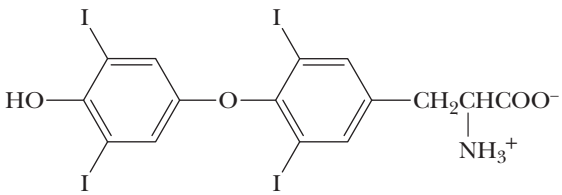


Ornithine

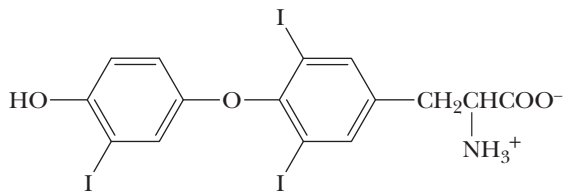


Citrulline

Thyroxine and triiodothyronine, two of several hormones derived from the amino acid tyrosine, are found in thyroid tissue:



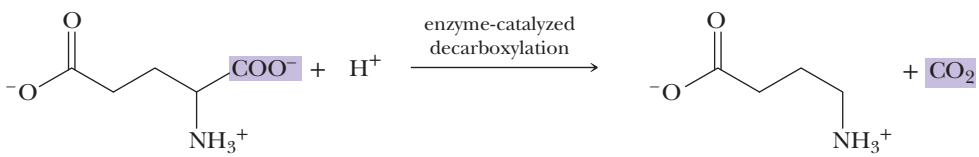
Thyroxine, T_4



Triiodothyronine, T_3

The principal function of these two hormones is to stimulate metabolism in other cells and tissues.

4-Aminobutanoic acid (γ-aminobutyric acid, or GABA) is found in high concentration (0.8 mM) in the brain, but in no significant amounts in any other mammalian tissue. GABA is synthesized in neural tissue by decarboxylation of the α-carboxyl group of glutamic acid and is a neurotransmitter in the central nervous system of invertebrates and possibly in humans as well:



Glutamic acid

4-Aminobutanoic acid (γ-Aminobutyric acid, GABA)

Only L-amino acids are found in proteins, and only rarely are D-amino acids a part of the metabolism of higher organisms. Several D-amino acids, however, along with their L-enantiomers, are found in lower forms of life. D-Alanine and D-glutamic acid, for example, are structural components of the cell walls of certain bacteria. Several D-amino acids are also found in peptide antibiotics.

18.3 What Are the Acid–Base Properties of Amino Acids?

A. Acidic and Basic Groups of Amino Acids

Among the most important chemical properties of amino acids are their acid–base properties. All are weak polyprotic acids because of the presence of both —COOH and $-NH_3^+$ groups. Given in Table 18.2 are pK_a values for each ionizable group of the 20 protein-derived amino acids.

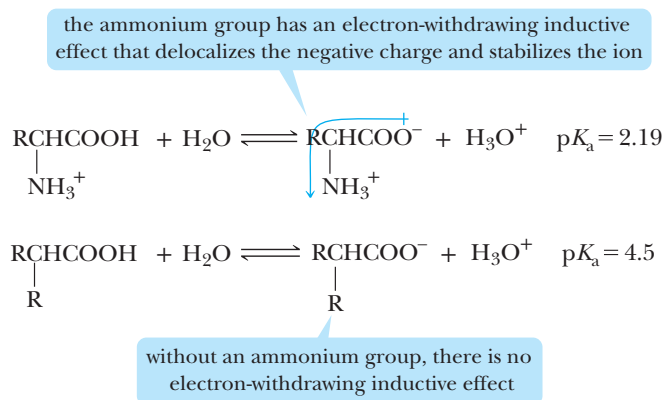
TABLE 18.2 pK_a Values for Ionizable Groups of Amino Acids

Amino Acid	pK_a of α-COOH	pK_a of α-NH_3^+	pK_a of Side Chain	Isoelectric Point (pI)
Alanine	2.35	9.87	–	6.11
Arginine	2.01	9.04	12.48	10.76
Asparagine	2.02	8.80	–	5.41
Aspartic acid	2.10	9.82	3.86	2.98
Cysteine	2.05	10.25	8.00	5.02
Glutamic acid	2.10	9.47	4.07	3.08
Glutamine	2.17	9.13	–	5.65
Glycine	2.35	9.78	–	6.06
Histidine	1.77	9.18	6.10	7.64
Isoleucine	2.32	9.76	–	6.04
Leucine	2.33	9.74	–	6.04
Lysine	2.18	8.95	10.53	9.74
Methionine	2.28	9.21	–	5.74
Phenylalanine	2.58	9.24	–	5.91
Proline	2.00	10.60	–	6.30
Serine	2.21	9.15	–	5.68
Threonine	2.09	9.10	–	5.60
Tryptophan	2.38	9.39	–	5.88
Tyrosine	2.20	9.11	10.07	5.63
Valine	2.29	9.72	–	6.00

Note: Dash indicates no ionizable side chain.

Acidity of α-Carboxyl Groups

The average value of the pK_a for an α-carboxyl group of a protonated amino acid is 2.19. Thus, the α-carboxyl group is a considerably stronger acid than the carboxyl group of acetic acid (pK_a 4.76) and other low-molecular-weight aliphatic carboxylic acids. This greater acidity is accounted for by the electron-withdrawing inductive effect of the adjacent $-NH_3^+$ group (recall that we used similar reasoning in Section 13.4A to account for the relative acidities of acetic acid and its mono-, di-, and trichloroderivatives):



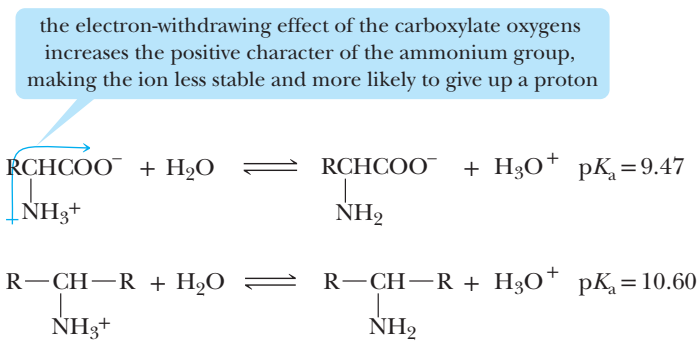
Acidity of Side-Chain Carboxyl Groups

Due to the electron-withdrawing inductive effect of the α-NH_3^+ group, the side-chain carboxyl groups of protonated aspartic acid and glutamic acid are also stronger acids than

acetic acid (pK_a 4.76). Notice that this acid-strengthening inductive effect decreases with increasing distance of the —COOH from the α-NH_3^+. Compare the acidities of the α-COOH of alanine (pK_a 2.35), the γ-COOH of aspartic acid (pK_a 3.86), and the δ-COOH of glutamic acid (pK_a 4.07).

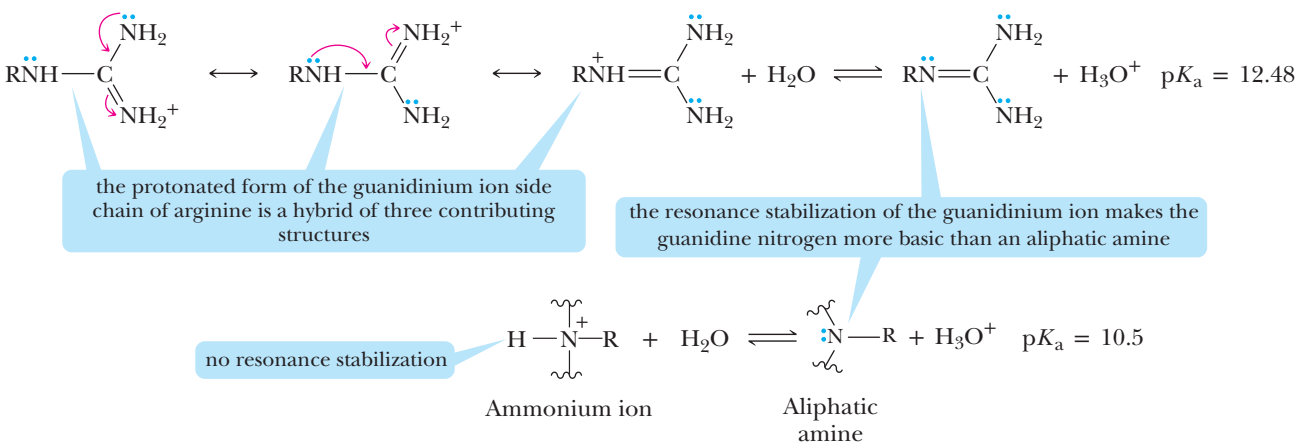
Acidity of α-Ammonium Groups

The average value of pK_a for an α-ammonium group, α-NH_3^+, is 9.47 compared with an average value of 10.76 for primary aliphatic ammonium ions (Section 10.4). Just as the —NH_3^+ group exerts an inductive effect on the carboxylate group, the electronegative oxygen atoms of the carboxylate group exert an electron-withdrawing inductive effect on the —NH_3^+ group. This increases the electron deficiency of the ammonium group, making it more likely to donate a proton to become an uncharged —NH_2 group. Thus, the α-ammonium group of an amino acid is a slightly stronger acid than a primary aliphatic ammonium ion. Conversely, an α-amino group is a slightly weaker base than a primary aliphatic amine.



Basicity of the Guanidine Group of Arginine

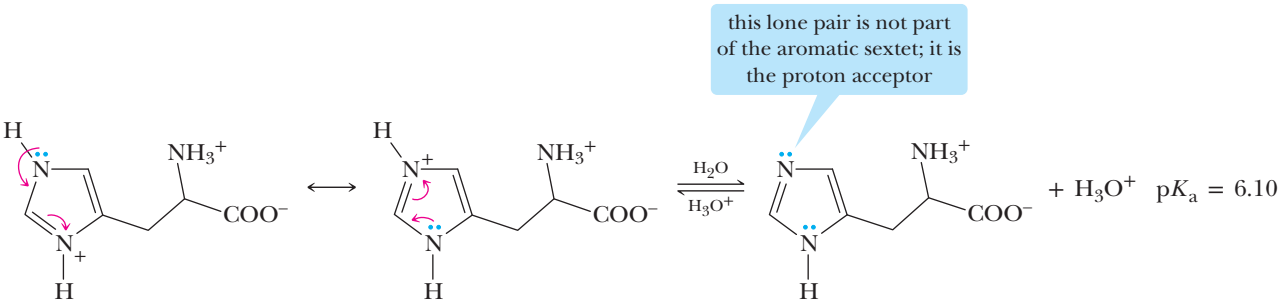
The side-chain guanidine group of arginine is a considerably stronger base than an aliphatic amine is. As we saw in Section 10.4, guanidine (pK_b 0.4) is the strongest base of any neutral compound. The remarkable basicity of the guanidine group of arginine is attributed to the large resonance stabilization of the protonated form.



Basicity of the Imidazole Group of Histidine

Because the imidazole group on the side chain of histidine contains six π electrons in a planar, fully conjugated ring, imidazole is classified as a heterocyclic aromatic amine (Section 9.2). The unshared pair of electrons on one nitrogen is a part of the aromatic sextet, whereas that on the other nitrogen is not. It is the pair of electrons that is not part

of the aromatic sextet that is responsible for the basic properties of the imidazole ring. Protonation of this nitrogen produces a resonance-stabilized cation:



Resonance-stabilized imidazolium cation

B. Titration of Amino Acids

Values of pK_a for the ionizable groups of amino acids are most commonly obtained by acid–base titration and by measuring the pH of the solution as a function of added base (or added acid, depending on how the titration is done). To illustrate this experimental procedure, consider a solution containing 1.00 mole of glycine to which has been added enough strong acid so that both the amino and carboxyl groups are fully protonated. Next, the solution is titrated with 1.00 M NaOH; the volume of base added and the pH of the resulting solution are recorded and then plotted as shown in Figure 18.3.

The most acidic group, and the one to react first with added sodium hydroxide, is the carboxyl group. When exactly 0.50 mole of NaOH has been added, the carboxyl group is half neutralized. At this point, the concentration of the zwitterion equals that of the positively charged ion, and the pH of 2.35 equals the pK_a of the carboxyl group (pK_{a1}):

$$\text{At pH} = pK_{a1} \qquad [H_3\overset{+}{N}CH_2COOH] = [H_3\overset{+}{N}CH_2COO^-]$$

Positive ion — Zwitterion

The end point of the first part of the titration is reached when one mole of NaOH has been added. At this point, the predominant species present is the zwitterion, and the observed pH of the solution is 6.06.

The next section of the curve represents titration of the $—NH_3^+$ group. When another 0.50 mole of NaOH has been added (bringing the total to 1.50 moles), half of the $—NH_3^+$ groups are neutralized and converted to $—NH_2$. At this point, the concentrations of the

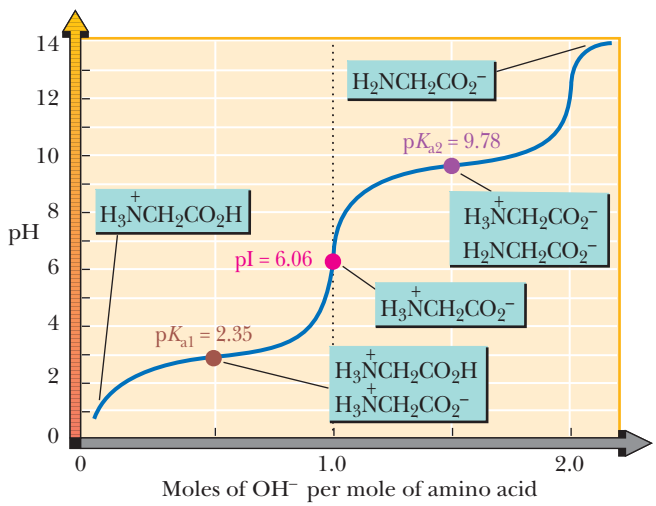


FIGURE 18.3 Titration of glycine with sodium hydroxide.

zwitterion and negatively charged ion are equal, and the observed pH is 9.78, the pK_a of the amino group of glycine (pK_{a2}):

$$\text{At pH} = pK_{a2} \qquad \underset{\text{Zwitterion}}{[H_3\overset{+}{N}CH_2COO^-]} = \underset{\text{Negative ion}}{[H_2\overset{+}{N}CH_2COO^-]}$$

The second end point of the titration is reached when a total of 2.00 moles of NaOH have been added and glycine is converted entirely to an anion.

C. Isoelectric Point

Titration curves such as that for glycine permit us to determine pK_a values for the ionizable groups of an amino acid. They also permit us to determine another important property: the **isoelectric point, pI**—the pH at which most of the molecules of the amino acid in solution have a net charge of zero. (They are zwitterions.) By examining the titration curve, you can see that the isoelectric point for glycine falls halfway between the pK_a values for the carboxyl and amino groups:

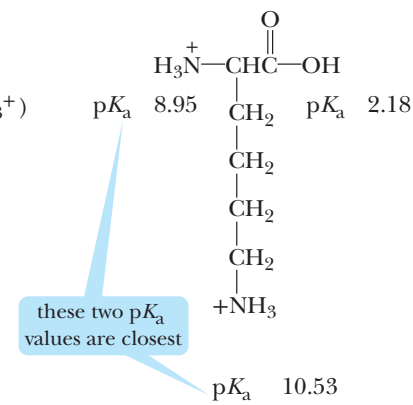
Isoelectric point (pI) The pH at which an amino acid, a polypeptide, or a protein has no net charge.

$$\text{pI} = \frac{1}{2}(pK_a\,\alpha\text{-COOH} + pK_a\,\alpha\text{-}NH_3^+)$$
$$= \frac{1}{2}(2.35 + 9.78) = 6.06$$

At pH 6.06, the predominant form of glycine molecules is the dipolar ion; furthermore, at this pH, the concentration of positively charged glycine molecules equals the concentration of negatively charged glycine molecules.

When estimating the pI for arginine, aspartic acid, glutamic acid, histidine, and lysine (amino acids that contain either two carboxyl or two ammonium groups), we use the pK_a's of the two groups that are closest in value. For example, the pI of lysine would be determined as follows:

$$\text{pI} = \tfrac{1}{2}(pK_a\,\alpha\text{-}\overset{+}{N}H_3 + pK_a\,\text{side chain-}NH_3^+)$$
$$= \tfrac{1}{2}(8.95 + 10.53) = 9.74$$



Given a value for the isoelectric point of an amino acid, it is possible to estimate the charge on that amino acid at any pH. For example, the charge on tyrosine at pH 5.63, the isoelectric point of tyrosine, is zero. A small fraction of tyrosine molecules is positively charged at pH 5.00 (0.63 unit less than its pI), and virtually all are positively charged at pH 3.63 (2.00 units less than its pI). As another example, the net charge on lysine is zero at pH 9.74. At pH values smaller than 9.74, an increasing fraction of lysine molecules is positively charged.

At pH values greater than pI, an increasing fraction of its molecules have a net negative charge. To summarize for any amino acid:

$$\underset{\text{pH} < \text{pI}\ (\text{net charge} = +)}{\underset{|}{\underset{NH_3^+}{RCHCOOH}}} \overset{OH^-}{\underset{H_3O^+}{\rightleftharpoons}} \underset{\text{pH} = \text{pI}\ (\text{net charge} = 0)}{\underset{|}{\underset{NH_3^+}{RCHCOO^-}}} \overset{OH^-}{\underset{H_3O^+}{\rightleftharpoons}} \underset{\text{pH} > \text{pI}\ (\text{net charge} = -)}{\underset{|}{\underset{NH_2}{RCHCOO^-}}}$$

HOW TO 18.1

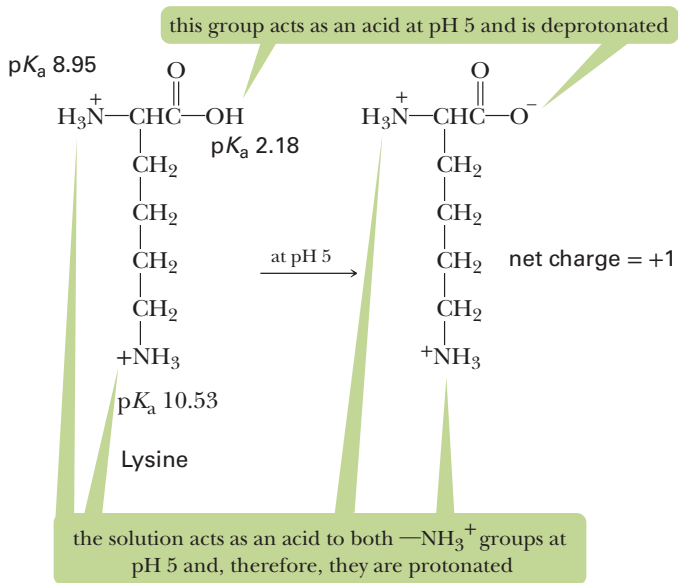
Approximate the Charge of an Amino Acid at Any Given pH

The pH of a solution is a measure of its acidity. The pK_a value of an ionizable functional group is a measure of the acidity of a proton on that functional group. In your study of general chemistry, you learned that the Henderson-Hasselbalch equation $\left(\text{pH} = \text{p}K_a + \log\dfrac{[\text{A}^-]}{[\text{HA}]}\right)$ allows us to relate the pH of a solution to the pK_a of an acid. The equation can be summarized as follows:*

(a) If the pH of the solution is lower than the pK_a of an acidic group, the solution behaves as an acid to the group and the group remains protonated.

(b) If the pH of the solution is higher than the pK_a of an acidic group, the acidic group behaves as an acid to the solution and the group is deprotonated.

We use lysine as an example. At pH 5, the charge on lysine will be +1:



*Note: This approximation works best when there is a difference of 1 unit between the pH value of the solution and the pK_a value of each ionizable group.

D. Electrophoresis

Electrophoresis The process of separating compounds on the basis of their electric charge.

Electrophoresis, a process of separating compounds on the basis of their electric charges, is used to separate and identify mixtures of amino acids and proteins. Electrophoretic separations can be carried out with paper, starch, agar, certain plastics, and cellulose acetate used as solid supports. In paper electrophoresis, a paper strip saturated with an aqueous buffer of predetermined pH serves as a bridge between two electrode vessels (Figure 18.4).

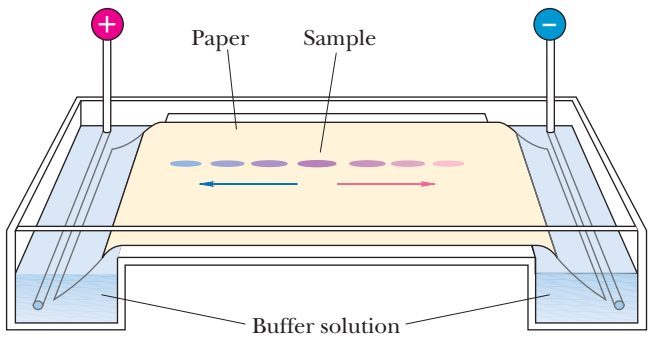
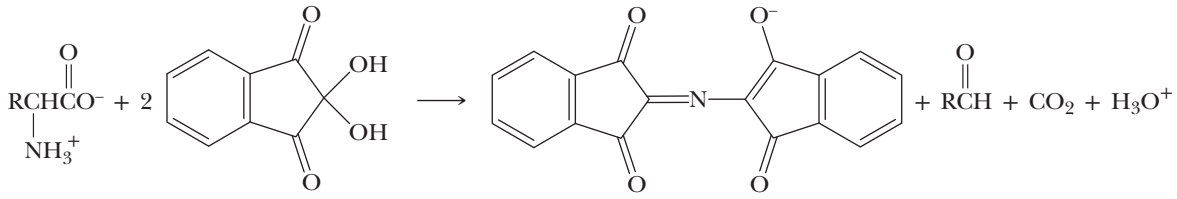


FIGURE 18.4
Electrophoresis of a mixture of amino acids. Those with a negative charge move toward the positive electrode; those with a positive charge move toward the negative electrode; those with no charge remain at the origin.

Next, a sample of amino acids is applied as a colorless spot on the paper strip. (The amino acid mixture is colorless.) When an electrical potential is then applied to the electrode vessels, amino acids migrate toward the electrode carrying the charge opposite to their own. Molecules having a high charge density move more rapidly than do those with a lower charge density. Any molecule already at its isoelectric point remains at the origin. After the separation is complete, the paper strip is sprayed with a dye that transforms each amino acid into a colored compound, making the separated components visible.

A dye commonly used to detect amino acids is ninhydrin (1,2,3-indanetrione monohydrate). Ninhydrin reacts with α-amino acids to produce an aldehyde, carbon dioxide, and a purple-colored anion:



An α-amino acid | Ninhydrin | Purple-colored anion

This reaction is commonly used in both qualitative and quantitative analysis of amino acids. Nineteen of the 20 protein-derived α-amino acids have primary amino groups and give the same purple-colored ninhydrin-derived anion. Proline, a secondary amine, gives a different, orange-colored compound.

EXAMPLE 18.2

The isoelectric point of tyrosine is 5.63. Toward which electrode does tyrosine migrate during paper electrophoresis at pH 7.0?

STRATEGY

At its isoelectric point, a molecule of an amino acid has no net charge. In a solution in which pH > pI, its molecules have a net negative charge, and in a solution in which pH < pI, its molecules have a net positive charge. Therefore, in this problem, the important point is to compare the pH of the solution and the pI of the amino acid.

SOLUTION

During paper electrophoresis at pH 7.0 (more basic than its isoelectric point), tyrosine has a net negative charge and migrates toward the positive electrode.

See problems 18.22, 18.23, 18.25, 18.26, 18.32, 18.33

PROBLEM 18.2

The isoelectric point of histidine is 7.64. Toward which electrode does histidine migrate during paper electrophoresis at pH 7.0?

EXAMPLE 18.3

The electrophoresis of a mixture of lysine, histidine, and cysteine is carried out at pH 7.64. Describe the behavior of each amino acid under these conditions.

STRATEGY

Compare the pI of each amino acid to the pH of the solution in which it is dissolved and determine the net charge on each at that pH. If the pI of the amino acid is identical to the pH of the solution in which it is dissolved, the amino acid will not migrate from the origin. If the pH of the solution is greater than its pI, an amino acid will migrate toward the positive electrode. If the pH of the solution is less than its pI, an amino acid will migrate toward the negative electrode.

SOLUTION

The isoelectric point of histidine is 7.64. At this pH, histidine has a net charge of zero and does not move from the origin. The pI of cysteine is 5.02; at pH 7.64 (more basic than its isoelectric point), cysteine has a net negative charge and moves toward the positive electrode. The pI of lysine is 9.74; at pH 7.64 (more acidic than its isoelectric point), lysine has a net positive charge and moves toward the negative electrode.

See problem 18.34

PROBLEM 18.3

Describe the behavior of a mixture of glutamic acid, arginine, and valine during paper electrophoresis at pH 6.0.

18.4 What Are Polypeptides and Proteins?

In 1902, Emil Fischer proposed that proteins were long chains of amino acids joined together by amide bonds formed between the α-carboxyl group of one amino acid and the α-amino group of another. For these amide bonds, Fischer proposed the special name **peptide bond**. Figure 18.5 shows the peptide bond formed between serine and alanine in the dipeptide serylalanine.

Peptide bond The special name given to the amide bond formed between the α-amino group of one amino acid and the α-carboxyl group of another amino acid.

Dipeptide A molecule containing two amino acid units joined by a peptide bond.

Tripeptide A molecule containing three amino acid units, each joined to the next by a peptide bond.

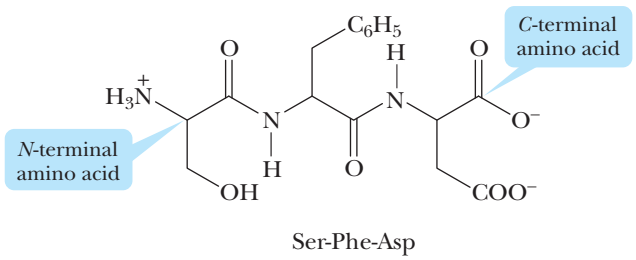
Polypeptide A macromolecule containing 20 or more amino acid units, each joined to the next by a peptide bond.

***N*-Terminal amino acid** The amino acid at the end of a polypeptide chain having the free $—NH_3^+$ group.

***C*-Terminal amino acid** The amino acid at the end of a polypeptide chain having the free $—COO^-$ group.

Peptide is the name given to a short polymer of amino acids. We classify peptides by the number of amino acid units in their chains. A molecule containing 2 amino acids joined by an amide bond is called a **dipeptide**. Those containing 3 to 10 amino acids are called **tripeptides**, **tetrapeptides**, **pentapeptides**, and so on. Molecules containing more than 10, but fewer than 20, amino acids are called **oligopeptides**. Those containing 20 or more amino acids are called **polypeptides**. **Proteins** are biological macromolecules with molecular weight 5,000 or greater and consisting of one or more polypeptide chains. The distinctions in this terminology are not at all precise.

By convention, polypeptides are written from left to right, beginning with the amino acid having the free $—NH_3^+$ group and proceeding toward the amino acid with the free $—COO^-$ group. The amino acid with the free $—NH_3^+$ group is called the ***N*-terminal amino acid**, and that with the free $—COO^-$ group is called the ***C*-terminal amino acid**:



Ser-Phe-Asp

Serine (Ser, S) + Alanine (Ala, A) → Serylalanine (Ser-Ala, S-A) + H_2O

FIGURE 18.5 The peptide bond in serylalanine.

EXAMPLE 18.4

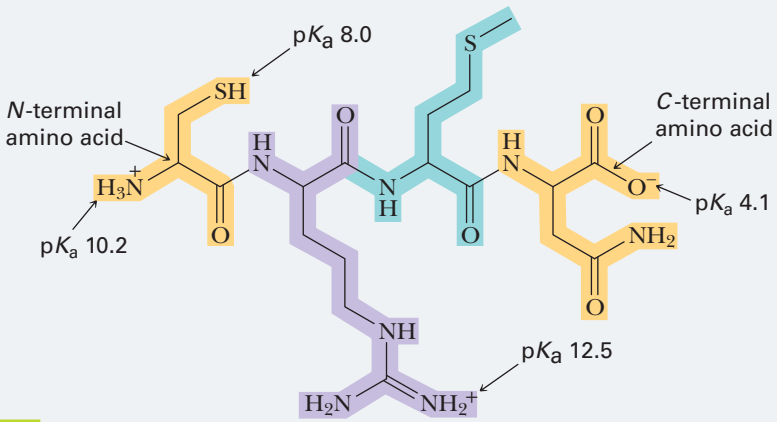
Draw a structural formula for Cys-Arg-Met-Asn. Label the *N*-terminal amino acid and the *C*-terminal amino acid. What is the net charge on this tetrapeptide at pH 6.0?

STRATEGY

Begin by drawing the zwitterion form of each amino acid in order from cysteine to asparagine, each oriented with its α-ammonium group on the left and its α-carboxylate group on the right. Then form peptide bonds by removing a water molecule from between $—COO^-$ and $^+H_3N—$ groups that are next to each other. To determine the net charge on this tetrapeptide, consult Table 18.2 for the pK_a value of the ionizable group on the side chain of each amino acid.

SOLUTION

The backbone of Cys-Arg-Met-Asn, a tetrapeptide, is a repeating sequence of nitrogen-α-carbon carbonyl. The net charge on this tetrapeptide at pH 6.0 is +1. The following is a structural formula for Cys-Arg-Met-Asn:



See problems 18.37, 18.41

PROBLEM 18.4

Draw a structural formula for Lys-Phe-Ala. Label the *N*-terminal amino acid and the *C*-terminal amino acid. What is the net charge on this tripeptide at pH 6.0?

18.5 What Is the Primary Structure of a Polypeptide or Protein?

The **primary (1°) structure** of a polypeptide or protein is the sequence of amino acids in its polypeptide chain. In this sense, the primary structure is a complete description of all covalent bonding in a polypeptide or protein.

Primary (1°) structure of proteins The sequence of amino acids in the polypeptide chain; read from the *N*-terminal amino acid to the *C*-terminal amino acid.

In 1953, Frederick Sanger of Cambridge University, England, reported the primary structure of the two polypeptide chains of the hormone insulin. Not only was this a remarkable achievement in analytical chemistry, but also it clearly established that the molecules of a given protein all have the same amino acid composition and the same amino acid sequence. Today, the amino acid sequences of over 20,000 different proteins are known, and the number is growing rapidly.

A. Amino Acid Analysis

The first step in determining the primary structure of a polypeptide is hydrolysis and quantitative analysis of its amino acid composition. Recall from Section 14.3D that amide

bonds are highly resistant to hydrolysis. Typically, a sample of a protein is hydrolyzed in 6 M HCl in a sealed glass vial at 110 °C for 24 to 72 hours. (This hydrolysis can be done in a microwave oven in a shorter time.) After the polypeptide is hydrolyzed, the resulting mixture of amino acids is analyzed by ion-exchange chromatography. In this process, the mixture of amino acids is passed through a specially packed column. Each of the 20 amino acids requires a different time to pass through the column. Amino acids are detected by reaction with ninhydrin as they emerge from the column (Section 18.3D), followed by absorption spectroscopy. Current procedures for the hydrolysis of polypeptides and the analysis of amino acid mixtures have been refined to the point where it is possible to determine the amino acid composition from as little as 50 nanomoles (50×10^{-9} mole) of a polypeptide. Figure 18.6 shows the analysis of a polypeptide hydrolysate by ion-exchange chromatography. Note that, during hydrolysis, the side-chain amide groups of asparagine and glutamine are hydrolyzed, and these amino acids are detected as aspartic acid and glutamic acid. For each glutamine or asparagine hydrolyzed, an equivalent amount of ammonium chloride is formed.

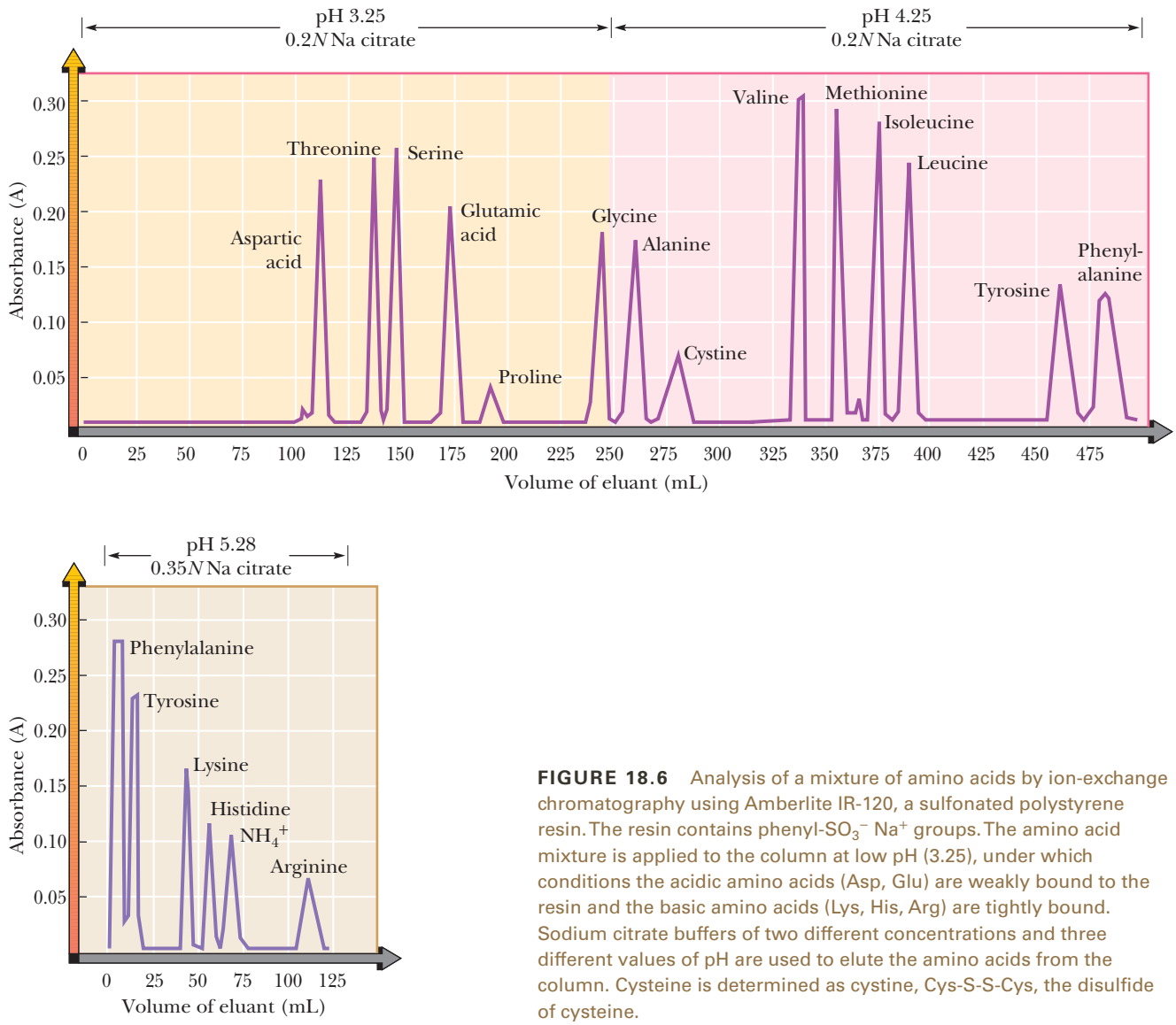


FIGURE 18.6 Analysis of a mixture of amino acids by ion-exchange chromatography using Amberlite IR-120, a sulfonated polystyrene resin. The resin contains phenyl-SO_3^- Na^+ groups. The amino acid mixture is applied to the column at low pH (3.25), under which conditions the acidic amino acids (Asp, Glu) are weakly bound to the resin and the basic amino acids (Lys, His, Arg) are tightly bound. Sodium citrate buffers of two different concentrations and three different values of pH are used to elute the amino acids from the column. Cysteine is determined as cystine, Cys-S-S-Cys, the disulfide of cysteine.

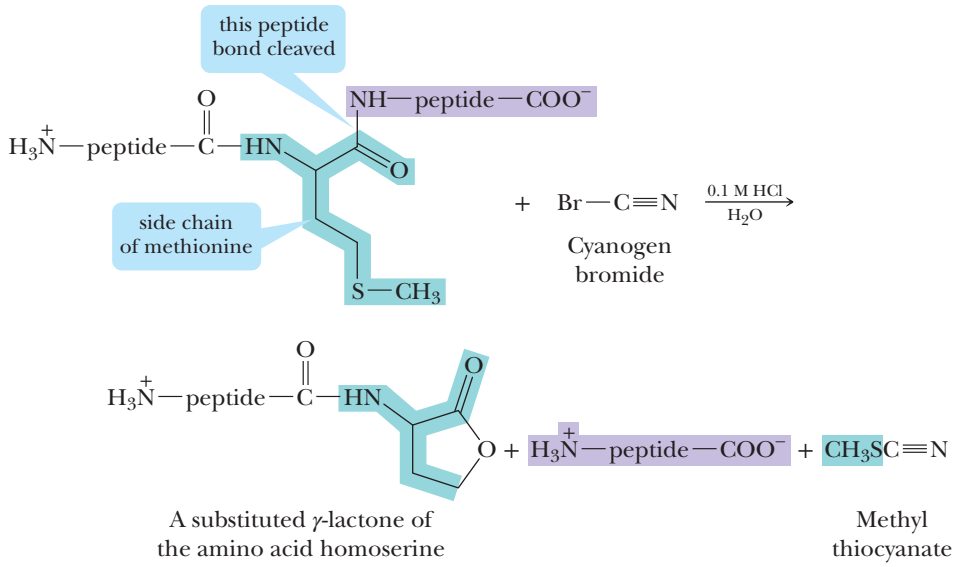


FIGURE 18.7 Cleavage by cyanogen bromide, BrCN, of a peptide bond formed by the carboxyl group of methionine.

B. Sequence Analysis

Once the amino acid composition of a polypeptide has been determined, the next step is to determine the order in which the amino acids are joined in the polypeptide chain. The most common sequencing strategy is to (1) cleave the polypeptide at specific peptide bonds (by using, for example, cyanogen bromide or certain proteolytic enzymes), (2) determine the sequence of each fragment (by using, for example, the Edman degradation), and then (3) match overlapping fragments to arrive at the sequence of the polypeptide.

Cyanogen Bromide

Cyanogen bromide (BrCN) is specific for the cleavage of peptide bonds formed by the carboxyl group of methionine (Figure 18.7). The products of this cleavage are substituted γ-lactones (Section 14.1C), derived from the *N*-terminal portion of the polypeptide, and a second fragment containing the *C*-terminal portion of the polypeptide.

Enzyme-Catalyzed Hydrolysis of Peptide Bonds

A group of proteolytic enzymes, including trypsin and chymotrypsin, can be used to catalyze the hydrolysis of specific peptide bonds. Trypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of Arg and Lys; chymotrypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of Phe, Tyr, and Trp.

Tom Strattman/AP Images

The diabetes drug, exenatide (top, trade name Byetta®), cannot be taken orally because stomach acid would immediately hydrolyze the peptide bonds.

EXAMPLE 18.5

Which of these tripeptides are hydrolyzed by trypsin? By chymotrypsin?

(a) Arg-Glu-Ser **(b)** Phe-Gly-Lys

STRATEGY

Trypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of Lys and Arg. Chymotrypsin catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of Phe, Tyr, and Trp.

SOLUTION

(a) The peptide bond between Arg and Glu is hydrolyzed in the presence of trypsin

$$\text{Arg-Glu-ser} + H_2O \xrightarrow{\text{trypsin}} \text{Arg} + \text{Glu-Ser}$$

Because none of these three aromatic amino acids is present in tripeptide (a), it is not affected by chymotrypsin.

(b) Tripeptide (b) is not affected by trypsin. Although Lys is present, its carboxyl group is at the *C*-terminal end and not involved in peptide bond formation. Tripeptide (b) is hydrolyzed in the presence of chymotrypsin.

$$\text{Phe-Gly-Lys} + H_2O \xrightarrow{\text{chymotrypsin}} \text{Phe} + \text{Gly-Lys}$$

See problem 18.39

PROBLEM 18.5

Which of these tripeptides are hydrolyzed by trypsin? By chymotrypsin?
(a) Tyr-Gln-Val **(b)** Thr-Phe-Ser **(c)** Thr-Ser-Phe

Edman Degradation

Edman degradation A method for selectively cleaving and identifying the *N*-terminal amino acid of a polypeptide chain.

Of the various chemical methods developed for determining the amino acid sequence of a polypeptide, the one most widely used today is the **Edman degradation**, introduced in 1950 by Pehr Edman of the University of Lund, Sweden. In this procedure, a polypeptide is treated with phenyl isothiocyanate, $C_6H_5N{=}C{=}S$, and then with acid. The effect of Edman degradation is to remove the *N*-terminal amino acid selectively as a substituted phenylthiohydantoin (Figure 18.8), which is then separated and identified.

The special value of the Edman degradation is that it cleaves the *N*-terminal amino acid from a polypeptide without affecting any other bonds in the chain. Furthermore, Edman degradation can be repeated on the shortened polypeptide, causing the next amino acid in the sequence to be cleaved and identified. In practice, it is possible to sequence as many as the first 20 to 30 amino acids in a polypeptide by this method, using as little as a few milligrams of material.

Most polypeptides in nature are longer than 20 to 30 amino acids, the practical limit on the number of amino acids that can be sequenced by repetitive Edman degradation. The special value of cleavage with cyanogen bromide, trypsin, and chymotrypsin is that, at specific peptide bonds, a long polypeptide chain can be cleaved into smaller polypeptide fragments, and each fragment can then be sequenced separately.

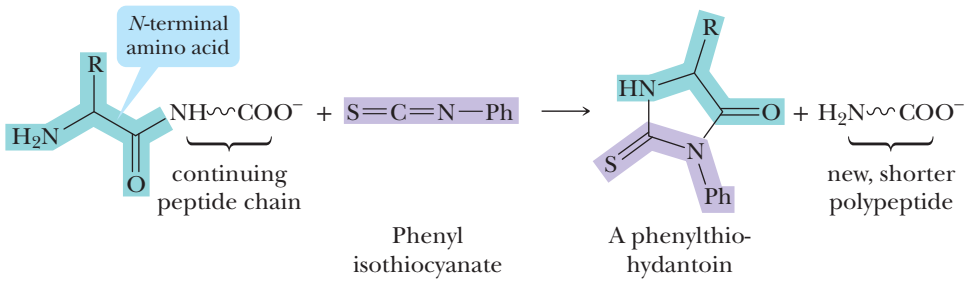


FIGURE 18.8 Edman degradation. Treatment of a polypeptide with phenyl isothiocyanate followed by acid selectively cleaves the *N*-terminal amino acid as a substituted phenylthiohydantoin.

EXAMPLE 18.6

Deduce the amino acid sequence of a pentapeptide from the following experimental results (note that, under the column "Amino Acids Determined from Procedure," the amino acids are listed in alphabetical order; in no way does this listing give any information about primary structure):

Experimental Procedure	Amino Acids Determined from Procedure
Amino Acid Analysis of Pentapeptide	Arg, Glu, His, Phe, Ser
Edman Degradation	Glu
Hydrolysis Catalyzed by Chymotrypsin	
Fragment A	Glu, His, Phe
Fragment B	Arg, Ser
Hydrolysis Catalyzed by Trypsin	
Fragment C	Arg, Glu, His, Phe
Fragment D	Ser

STRATEGY

Review the specificity of each method of degradation:

- Edman degradation: Selectively cleaves the *N*-terminal amino acid.
- Chymotrypsin: Cleaves the peptide bonds formed by the carboxyl groups of Phe, Tyr, and Trp.
- Trypsin: Cleaves the peptide bonds formed by the carboxyl groups of Arg and Lys.

SOLUTION

Edman degradation cleaves Glu from the pentapeptide; therefore, glutamic acid must be the *N*-terminal amino acid, and we have

$$\text{Glu-}(\text{Arg, His, Phe, Ser})$$

Fragment A from chymotrypsin-catalyzed hydrolysis contains Phe. Because of the specificity of chymotrypsin, Phe must be the *C*-terminal amino acid of fragment A. Fragment A also contains Glu, which we already know is the *N*-terminal amino acid. From these observations, we conclude that the first three amino acids in the chain must be Glu-His-Phe, and we now write the following partial sequence:

$$\text{Glu-His-Phe-}(\text{Arg, Ser})$$

The fact that trypsin cleaves the pentapeptide means that Arg must be within the pentapeptide chain; it cannot be the *C*-terminal amino acid. Therefore, the complete sequence must be

$$\text{Glu-His-Phe-Arg-Ser}$$

See problems 18.38, 18.40

PROBLEM 18.6

Deduce the amino acid sequence of an undecapeptide (11 amino acids) from the experimental results shown in the following table:

Experimental Procedure	Amino Acids Determined from Procedure
Amino Acid Analysis of Undecapeptide	Ala, Arg, Glu, Lys_2, Met, Phe, Ser, Thr, Trp, Val
Edman Degradation	Ala
Trypsin-Catalyzed Hydrolysis	
Fragment E	Ala, Glu, Arg
Fragment F	Thr, Phe, Lys
Fragment G	Lys
Fragment H	Met, Ser, Trp, Val
Chymotrypsin-Catalyzed Hydrolysis	
Fragment I	Ala, Arg, Glu, Phe, Thr
Fragment J	Lys_2, Met, Ser, Trp, Val
Treatment with Cyanogen Bromide	
Fragment K	Ala, Arg, Glu, Lys_2, Met, Phe, Thr, Val
Fragment L	Trp, Ser

18.6 What Are the Three-Dimensional Shapes of Polypeptides and Proteins?

A. Geometry of a Peptide Bond

In the late 1930s, Linus Pauling began a series of studies aimed at determining the geometry of a peptide bond. One of his first discoveries was that a peptide bond is planar. As shown in Figure 18.9, the four atoms of a peptide bond and the two α-carbons joined to it all lie in the same plane.

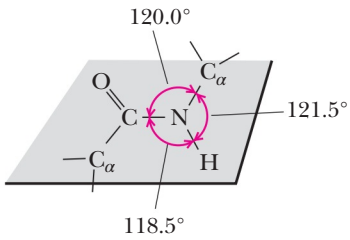
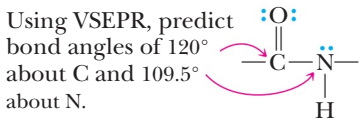
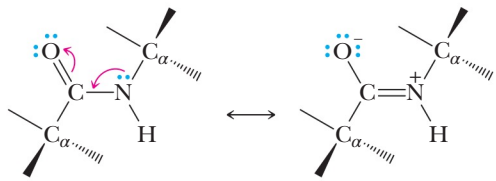


FIGURE 18.9 Planarity of a peptide bond. Bond angles about the carbonyl carbon and the amide nitrogen are approximately 120°.

Had you been asked in Chapter 1 to describe the geometry of a peptide bond, you probably would have predicted bond angles of 120° about the carbonyl carbon and 109.5° about the amide nitrogen.



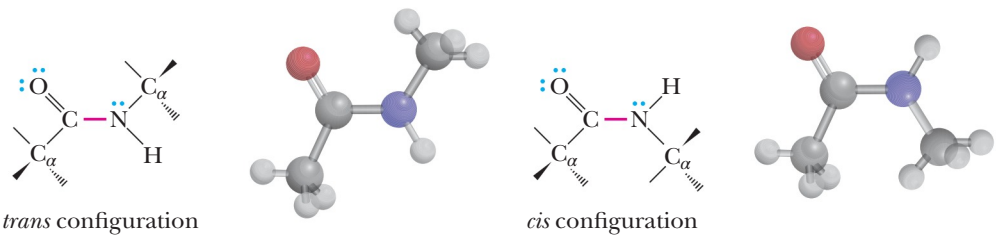
This prediction agrees with the observed bond angles of approximately 120° about the carbonyl carbon. It does not agree, however, with the observed bond angles of 120° about the amide nitrogen. To account for the observed geometry, Pauling proposed that a peptide bond is more accurately represented as a resonance hybrid of these two contributing structures:



(1) (2)

Contributing structure (1) shows a carbon–oxygen double bond, and structure (2) shows a carbon–nitrogen double bond. The hybrid, of course, is neither of these. In the real structure, the carbon–nitrogen bond has considerable double-bond character. Accordingly, in the hybrid, the six-atom group of the peptide bond and the two attached α-carbons are planar.

Two configurations are possible for the atoms of a planar peptide bond. In one, the two α-carbons are *cis* to each other; in the other, they are *trans* to each other. The *trans* configuration is more favorable because the α-carbons with the bulky groups bonded to them are farther from each other than they are in the *cis* configuration. Virtually all peptide bonds in naturally occurring proteins studied to date have the *trans* configuration.



trans configuration *cis* configuration

B. Secondary Structure

Secondary (2°) structure of proteins The ordered arrangements (conformations) of amino acids in localized regions of a polypeptide or protein.

Secondary (2°) structure is the ordered arrangement (conformation) of amino acids in localized regions of a polypeptide or protein molecule. The first studies of polypeptide conformations were carried out by Linus Pauling and Robert Corey, beginning in 1939. They assumed that, in conformations of greatest stability, all atoms in a peptide bond lie in the same plane and there is **hydrogen bonding** between the N—H of one peptide bond and the C═O of another, as shown in Figure 18.10.

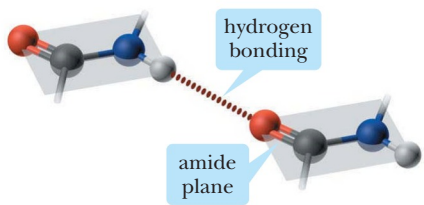


FIGURE 18.10 Hydrogen bonding between amide groups.

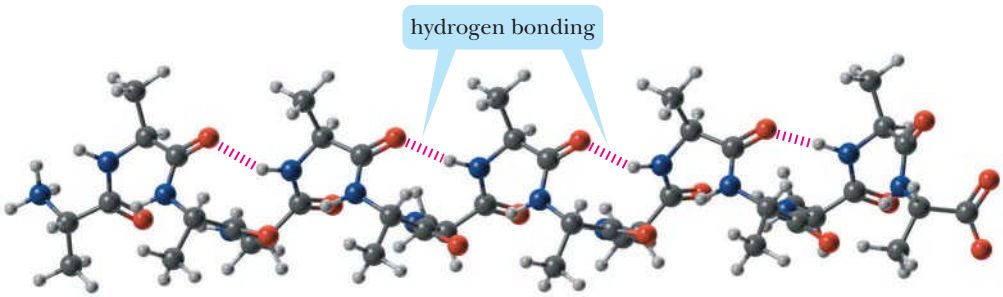


FIGURE 18.11 An α-helix. The polypeptide chain is repeating units of L-alanine.

On the basis of model building, Pauling proposed that two types of secondary structure should be particularly stable: the α-helix and the antiparallel β-pleated sheet.

The α-Helix

In the **α-helix** pattern, shown in Figure 18.11, a polypeptide chain is coiled in a spiral. As you study this section of the α-helix, note the following:

α-Helix A type of secondary structure in which a section of polypeptide chain coils into a spiral, most commonly a right-handed spiral.

1. The helix is coiled in a clockwise, or right-handed, manner. *Right-handed* means that if you turn the helix clockwise, it twists away from you. In this sense, a right-handed helix is analogous to the right-handed thread of a common wood or machine screw.
2. There are 3.6 amino acids per turn of the helix.
3. Each peptide bond is *trans* and planar.
4. The N—H group of each peptide bond points roughly downward, parallel to the axis of the helix, and the C═O of each peptide bond points roughly upward, also parallel to the axis of the helix.
5. The carbonyl group of each peptide bond is hydrogen bonded to the N—H group of the peptide bond four amino acid units away from it. Hydrogen bonds are shown as dotted lines.
6. All R— groups point outward from the helix.

Almost immediately after Pauling proposed the α-helix conformation, other researchers proved the presence of α-helix conformations in keratin, the protein of hair and wool. It soon became obvious that the α-helix is one of the fundamental folding patterns of polypeptide chains.

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The star cucumber, *Sicyos angulatus*, uses left-handed helical tendrils to attach itself to climbing vines. Its helical pattern is analogous, but in reverse, to the right-handed α-helix of polypeptides.

The β-Pleated Sheet

An antiparallel **β-pleated sheet** consists of an extended polypeptide chain with neighboring sections of the chain running in opposite (antiparallel) directions. In a parallel β-pleated sheet, the neighboring sections run in the same direction. Unlike the α-helix arrangement, N—H and C═O groups lie in the plane of the sheet and are roughly perpendicular to the long axis of the sheet. The C═O group of each peptide bond is hydrogen bonded to the N—H group of a peptide bond of a neighboring section of the chain (Figure 18.12).

As you study this section of β-pleated sheet in Figure 18.12 note the following:

β-Pleated sheet A type of secondary structure in which two sections of polypeptide chain are aligned parallel or antiparallel to one another.

1. The three sections of the polypeptide chain lie adjacent to each other and run in opposite (antiparallel) directions.
2. Each peptide bond is planar, and the α-carbons are *trans* to each other.
3. The C═O and N—H groups of peptide bonds from adjacent sections point at each other and are in the same plane, so that hydrogen bonding is possible between adjacent sections.
4. The R— groups on any one chain alternate, first above, then below, the plane of the sheet, and so on.

The β-pleated sheet conformation is stabilized by hydrogen bonding between N—H groups of one section of the chain and C═O groups of an adjacent section. By comparison, the α-helix is stabilized by hydrogen bonding between N—H and C═O groups within the same polypeptide chain.

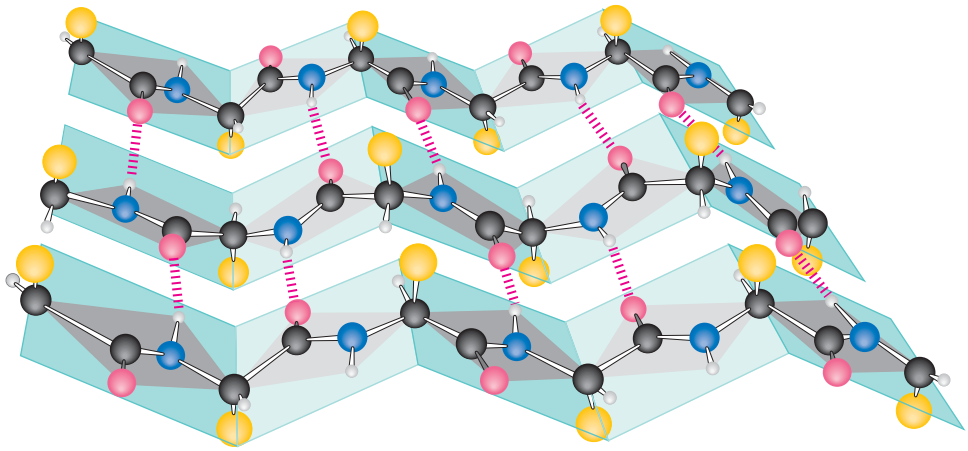


FIGURE 18.12 β-Pleated sheet conformation with three polypeptide chains running in opposite (antiparallel) directions. Hydrogen bonding between chains is indicated by dashed lines.

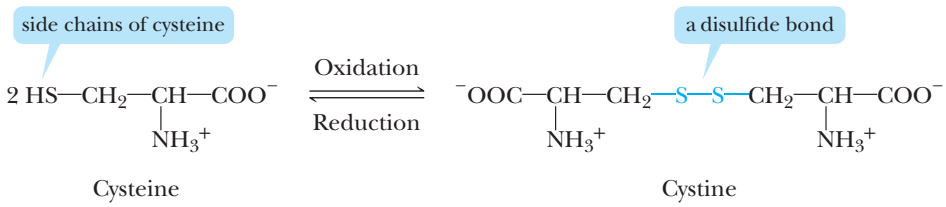
C. Tertiary Structure

Tertiary (3°) structure of proteins The three-dimensional arrangement in space of all atoms in a single polypeptide chain.

Tertiary (3°) structure is the overall folding pattern and arrangement in space of all atoms in a single polypeptide chain. No sharp dividing line exists between secondary and tertiary structures. Secondary structure refers to the spatial arrangement of amino acids *close to one another* on a polypeptide chain, whereas tertiary structure refers to the three-dimensional arrangement of *all* atoms in a polypeptide chain. Among the most important factors in maintaining 3° structure are disulfide bonds, hydrophobic interactions, hydrogen bonding, and salt bridges.

Disulfide bond A covalent bond between two sulfur atoms; an —S—S— bond.

Disulfide bonds play an important role in maintaining tertiary structure. Disulfide bonds are formed between side chains of two cysteine units by oxidation of their thiol groups (—SH) to form a disulfide bond (Section 8.6B). Treatment of a disulfide bond with a reducing agent regenerates the thiol groups:



Perms are created using chemicals that break and make disulfide bonds between different protein strands in hair

Figure 18.13 shows the amino acid sequence of human insulin. This protein consists of two polypeptide chains: an A chain of 21 amino acids and a B chain of 30 amino acids. The A chain is bonded to the B chain by two interchain disulfide bonds. An intrachain disulfide bond also connects the cysteine units at positions 6 and 11 of the A chain.

As an example of 2° and 3° structure, let us look at the three-dimensional structure of myoglobin, a protein found in skeletal muscle and particularly abundant in diving mammals, such as seals, whales, and porpoises. Myoglobin and its structural relative, hemoglobin, are the oxygen transport and storage molecules of vertebrates. Hemoglobin binds molecular oxygen in the lungs and transports it to myoglobin in muscles. Myoglobin stores molecular oxygen until it is required for metabolic oxidation.

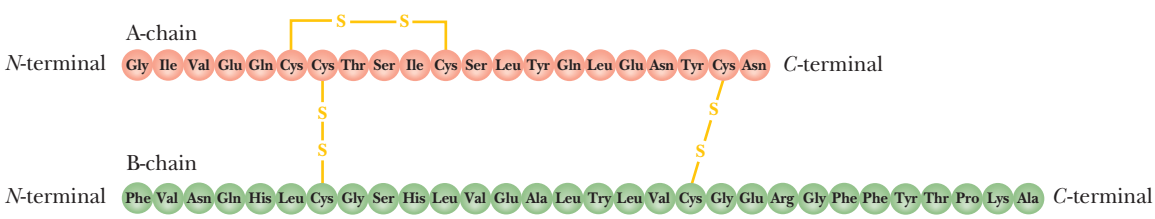
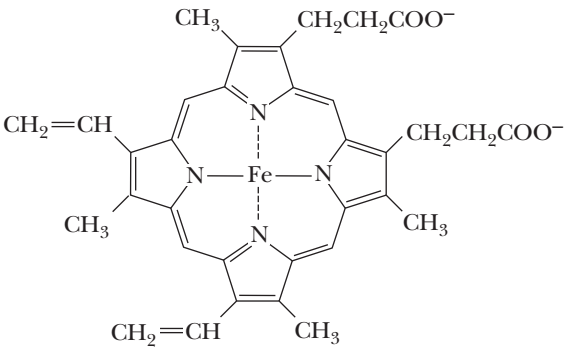


FIGURE 18.13 Human insulin. The A chain of 21 amino acids and B chain of 30 amino acids are connected by interchain disulfide bonds between A7 and B7 and between A20 and B19. In addition, a single intrachain disulfide bond occurs between A6 and A11.



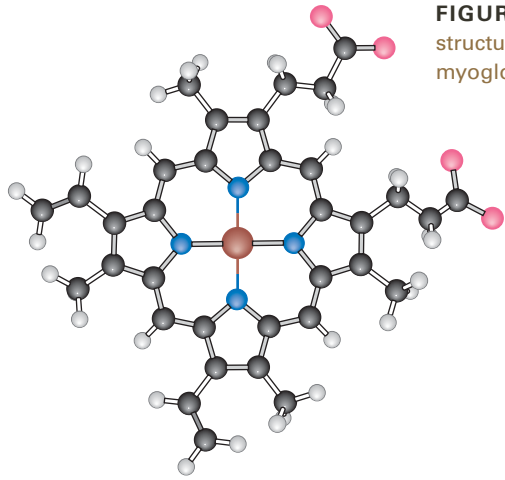


FIGURE 18.14 The structure of heme, found in myoglobin and hemoglobin.

Myoglobin consists of a single polypeptide chain of 153 amino acids. Myoglobin also contains a single heme unit. Heme consists of one Fe^{2+} ion, coordinated in a square planar array with the four nitrogen atoms of a molecule of porphyrin (Figure 18.14).

Determination of the three-dimensional structure of myoglobin represented a milestone in the study of molecular architecture. For their contribution to this research, John C. Kendrew and Max F. Perutz, both of Britain, shared the 1962 Nobel Prize for Chemistry. The secondary and tertiary structures of myoglobin are shown in Figure 18.15. The single polypeptide chain is folded into a complex, almost boxlike shape.

Important structural features of the three-dimensional shape of myoglobin are as follows:

© Rod Kaye/iStockphoto

The humpback whale relies on myoglobin as a storage form of oxygen.

1. The backbone consists of eight relatively straight sections of α-helix, each separated by a bend in the polypeptide chain. The longest section of α-helix has 24 amino acids, the shortest has seven. Some 75% of the amino acids are found in these eight regions of α-helix.

2. Hydrophobic side chains of phenylalanine, alanine, valine, leucine, isoleucine, and methionine are clustered in the interior of the molecule, where they are shielded from contact with water. **Hydrophobic interactions** are a major factor in directing the folding of the polypeptide chain of myoglobin into this compact, three-dimensional shape.

3. The outer surface of myoglobin is coated with hydrophilic side chains, such as those of lysine, arginine, serine, glutamic acid, histidine, and glutamine, which interact with the aqueous environment by **hydrogen bonding**. The only polar side chains that point to the interior of the myoglobin molecule are those of two histidine units, which point inward toward the heme group.

4. Oppositely charged amino acid side chains close to each other in the three-dimensional structure interact by electrostatic attractions called **salt bridges**. An example of a salt bridge is the attraction of the side chains of lysine ($—NH_3^+$) and glutamic acid ($—COO^-$).

The tertiary structures of hundreds of proteins have also been determined. It is clear that proteins contain α-helix and β-pleated sheet structures, but that wide variations exist in the relative amounts of each. Lysozyme, with 129 amino acids in a single polypeptide chain, has only 25% of its amino acids in α-helix regions. Cytochrome, with 104 amino acids in a single polypeptide chain, has no α-helix structure but does contain several regions of β-pleated sheet. Yet, whatever the proportions of α-helix, β-pleated sheet, or other periodic structure, virtually all nonpolar side chains of water-soluble proteins are directed toward the interior of the molecule, whereas polar side chains are on the surface of the molecule, in contact with the aqueous environment.

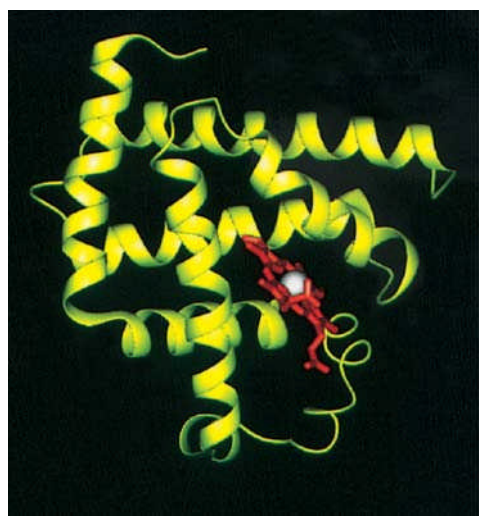


FIGURE 18.15 Ribbon model of myoglobin. The polypeptide chain is shown in yellow, the heme ligand in red, and the Fe atom as a white sphere.

EXAMPLE 18.7

With which of the following amino acid side chains can the side chain of threonine form hydrogen bonds?

(a) Valine
(b) Asparagine
(c) Phenylalanine
(d) Histidine
(e) Tyrosine
(f) Alanine

STRATEGY

Analyze the types of side chains of these amino acids and then look for potential interactions between them by hydrogen bonding.

SOLUTION

The side chain of threonine contains a hydroxyl group that can participate in hydrogen bonding in two ways: (1) Its oxygen has a partial negative charge and can function as a hydrogen bond acceptor; (2) its hydrogen has a partial positive charge and can function as a hydrogen bond donor. Therefore, the side chain of threonine can form hydrogen bonds with the side chains of tyrosine, asparagine, and histidine.

See problem 18.47

PROBLEM 18.7

At pH 7.4, with what amino acid side chains can the side chain of lysine form salt bridges?

D. Quaternary Structure

Quaternary (4°) structure of proteins The arrangement of polypeptide monomers into a noncovalently bonded aggregation.

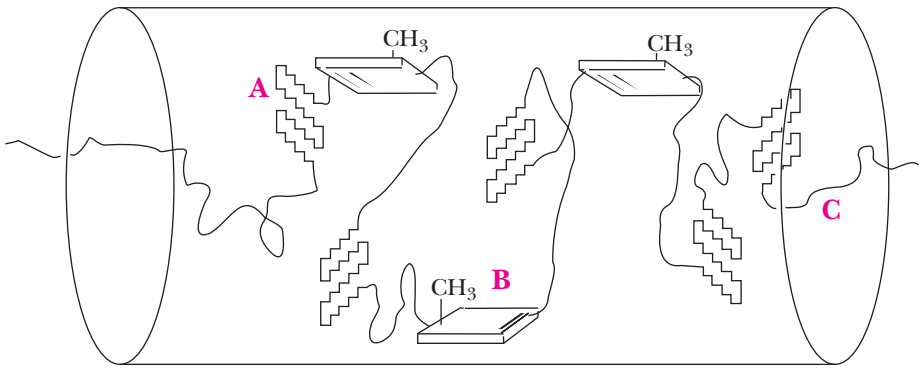
Most proteins with molecular weight greater than 50,000 consist of two or more noncovalently linked polypeptide chains. The arrangement of protein monomers into an aggregation is known as **quaternary (4°) structure**. A good example is hemoglobin (Figure 18.16), a protein that consists of four separate polypeptide chains: two α-chains of 141 amino acids each and two β-chains of 146 amino acids each.

Chemical Connections 18A

SPIDER SILK: A CHEMICAL AND ENGINEERING WONDER OF NATURE

Many of society's technological innovations have been inspired by nature. Velcro, for example, is modeled after plant burrs. The water-repellent swimsuits that revolutionized the sport of swimming were modeled after the skin of sharks. And hundreds of medicines are based on natural products. However, one product of nature that for centuries has been difficult to harness or imitate is spider silk. A strand of spider silk is almost five times stronger than a strand of steel with the same diameter. In addition to its strength, a strand of spider silk can be stretched up to 30–40% of its length without breaking. As shown in the following graphic of its secondary structure, a strand of spider silk consists of oriented amorphous regions (**A**), crystalline regions (**B**), and completely amorphous regions (**C**). The oriented amorphous regions are held together by hydrogen bonds and give spider silk its elasticity. The crystalline regions are mostly responsible for the strength of spider silk. They consist of β-pleated sheets and are highly hydrophobic, which also makes spider silk insoluble in water and resistant to rain and dew.

For centuries, spider silk has been highly sought after for its properties. Unfortunately, spiders are solitary animals and, unlike silkworms, cannot be domesticated. This leaves only one option for harnessing the utility of spider silk: its reproduction using artificial means. Research thus far has revealed the detailed structure of spider silk. However, it is a testament to the elegance of nature that despite the fact that spider silk consists mostly of alanine and glycine, researchers have yet to find a way to assemble a strand of spider silk in the laboratory. Incidentally, after a spider web has lost its stickiness, most spiders "recycle" the protein by eating their webs, leaving nary a trace of this chemical and engineering wonder of nature.



Question

Draw two pentapeptide strands of polyalanine and show how they can hydrogen-bond to each other.

The major factor stabilizing the aggregation of protein subunits is the **hydrophobic effect**. When separate polypeptide chains fold into compact three-dimensional shapes to expose polar side chains to the aqueous environment and shield nonpolar side chains from water, hydrophobic "patches" may still appear on the surface, in contact with water. These patches can be shielded from water if two or more monomers assemble so that their hydrophobic patches are in contact. The numbers of subunits of several proteins of known quaternary structure are shown in Table 18.3.

Hydrophobic effect The tendency of nonpolar groups to cluster in such a way as to be shielded from contact with an aqueous environment.

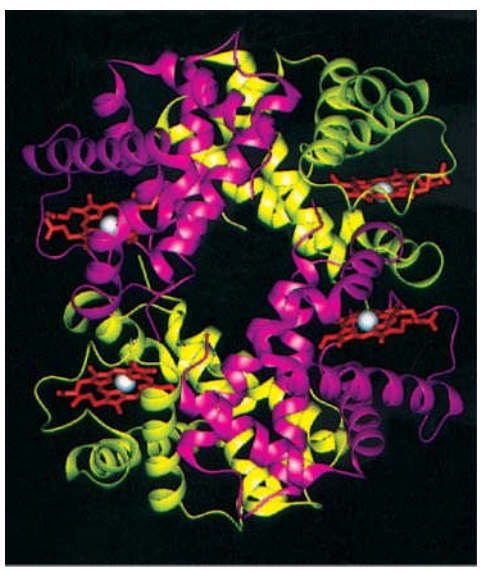


FIGURE 18.16 Ribbon model of hemoglobin. The α-chains are shown in purple, the β-chains in yellow, the heme ligands in red, and the Fe atoms as white spheres.

TABLE 18.3 Quaternary Structure of Selected Proteins

Protein	Number of Subunits
Alcohol dehydrogenase	2
Aldolase	4
Hemoglobin	4
Lactate dehydrogenase	4
Insulin	6
Glutamine synthetase	12
Tobacco mosaic virus protein disc	17

SUMMARY OF KEY QUESTIONS

18.1 What Are the Many Functions of Proteins?

Proteins have many roles in growth and metabolism, among which are:

- Structural (collagen)
- Catalytic (trypsin and other digestive enzymes)
- Transport (hemoglobin)
- Movement (myosin and actin)
- Protection (immunoglobulins)
- Hormonal (insulin)

18.2 What Are Amino Acids?

- **α-Amino acids** are compounds that contain an amino group alpha to a carboxyl group.
- Each amino acid has an acid (a —COOH group) and a base (an $—NH_2$ group) that undergo an acid–base reaction to form an internal salt given the special name **zwitterion**. A zwitterion has no net charge because it contains one positive charge and one negative charge.
- With the exception of glycine, all protein-derived amino acids are chiral.
- Whereas most monosaccharides in the biological world have the D-configuration, the vast majority of naturally occurring α-amino acids have the L-configuration at the α-carbon. D-amino acids are rare.
- Isoleucine and threonine contain a second stereocenter, and four stereoisomers are possible for each.
- The 20 protein-derived amino acids are commonly divided into four categories: nine with nonpolar side chains, four with polar but un-ionized side chains, four with acidic side chains, and three with basic side chains.

18.3 What Are the Acid–Base Properties of Amino Acids?

- Amino acids are weak polyprotic acids because of their —COOH and $—NH_3^+$ groups.
- The average value of pK_a for an α-carboxyl group of a protonated amino acid is 2.19. Thus the α-carboxyl group is a considerably stronger acid than the carboxyl group of acetic acid (pK_a 4.76), a fact due to the electron-withdrawing inductive effect of the nearby $—NH_3^+$ group of the α-amino acid.
- The average value of pK_a for an α-ammonium group is 9.47, compared to an average value of 10.76 for a primary aliphatic ammonium ion. Thus, the α-ammonium group of an amino acid is a slightly stronger acid than a primary aliphatic amine.
- The side-chain guanidine group of arginine is a considerably stronger base than an aliphatic amine. This remarkable basicity is attributed to the large resonance stabilization of the protonated form relative to the neutral form.
- The **isoelectric point**, **pI**, of an amino acid, polypeptide, or protein is the pH at which the majority of its molecules have no net charge.
- **Electrophoresis** is the process of separating compounds on the basis of their electric charge. Compounds with a higher charge density move more rapidly than those with a lower charge density.
- Any amino acid or protein in a solution with a pH that equals the pI of the compound remains at the origin. One with a net negative charge moves toward the positive electrode, and one with a net positive charge moves toward the negative electrode.

18.4 What Are Polypeptides and Proteins?

- A **peptide bond** is the special name given to the amide bond formed between α-amino acids.
- A **polypeptide** is a biological macromolecule containing 20 or more amino acids joined by peptide bonds.
- By convention, the sequence of amino acids in a polypeptide is written from the ***N*-terminal amino acid** toward the ***C*-terminal amino acid**.
- A **peptide bond** is planar; that is, the four atoms of the amide bond and the two α-carbons bonded to it lie in the same plane.
- Bond angles about the amide nitrogen and the carbonyl carbon of a peptide bond are approximately 120°.

18.5 What Is the Primary Structure of a Polypeptide or Protein?

- The **primary (1°) structure** of a polypeptide or protein refers to the sequence of amino acids in its polypeptide chain.
- The first step in determination of primary structure is hydrolysis and quantitative analysis of amino acid composition by **ion-exchange chromatography**.
- **Cyanogen bromide** is specific for the cleavage of peptide bonds formed by the carboxyl group of methionine.
- **Trypsin** catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of arginine and lysine.
- **Chymotrypsin** catalyzes the hydrolysis of peptide bonds formed by the carboxyl groups of phenylalanine, tyrosine, and tryptophan.
- The **Edman degradation** selectively cleaves the *N*-terminal amino acid without affecting any other peptide bonds in a polypeptide or protein.

18.6 What Are the Three-Dimensional Shapes of Polypeptides and Proteins?

- The four atoms of a peptide bond and the two α-carbons bonded to it all lie in the same plane; that is, a peptide bond is planar.
- **Secondary (2°) structure** refers to the ordered arrangement (conformations) of amino acids in localized regions of a polypeptide or protein. The two most prevalent types of secondary structure are the α-helix and the β-pleated sheet, both of which are stabilized by hydrogen bonding.
- In an **α-helix**, the carbonyl group of each peptide bond is hydrogen-bonded to the N—H group of the peptide bond four amino acids away from it.
- In an **antiparallel β-pleated sheet**, neighboring sections of a polypeptide chain run in opposite (antiparallel) directions, and the C═O group of each peptide bond is hydrogen-bonded to the N—H group of a peptide bond in a section of the neighboring antiparallel chain.
- In a **parallel β-pleated sheet**, the neighboring sections of the polypeptide chain run in the same (parallel) directions, and the C═O of each peptide bond is hydrogen-bonded to the N—H group of a peptide bond in a neighboring section of the chain.
- **Tertiary (3°) structure** refers to the overall folding pattern and arrangement in space of all atoms in a single polypeptide chain.
- **Quaternary (4°) structure** is the arrangement of individual polypeptide chains into a noncovalently bonded aggregate. A major factor stabilizing quaternary structure is hydrophobic interaction created when separate polypeptide chains fold into compact three-dimensional shapes that expose their polar side chains to the aqueous environment and shield their nonpolar side chains from the aqueous environment. Any remaining exposed hydrophobic patches can be shielded from water if two or more polypeptide chains assemble so that their hydrophobic patches are in contact.

QUICK QUIZ

Answer true or false to the following questions to assess your general knowledge of the concepts in this chapter. If you have difficulty with any of them, you should review the appropriate section in the chapter (shown in parentheses) before attempting the more challenging end-of-chapter problems.

1. The isoelectric point of an amino acid is the pH at which the majority of molecules in solution have a net charge of –1. (18.3)
2. Proteins can protect an organism against disease. (18.1)
3. Titration of an amino acid can be used to determine both the pK_a of its ionizable groups and its isoelectric point. (18.3)
4. Hydrogen bonding, salt bridges, hydrophobic interactions, and disulfide bonds can each be categorized as stabilizing factors in a protein. (18.6)
5. A polypeptide chain is read from its *C*-terminal end to its *N*-terminal end. (18.5)
6. The majority of naturally occurring amino acids are from the D-series. (18.2)
7. The amino group of an α-amino acid is more basic than the amino group of an aliphatic amine. (18.3)
8. Lysine contains a basic side chain. (18.2)
9. Electrophoresis is the process of creating a synthetic protein. (18.3)
10. A peptide bond exhibits free rotation at room temperature. (18.6)
11. In Edman degradation, a polypeptide is shortened one amino acid at a time using the reagent phenyl isothiocyanate. (18.5)
12. Phenylalanine contains a polar side chain. (18.2)
13. The side chain of arginine shows enhanced basicity because of resonance stabilization of the ion that results after protonation. (18.3)
14. α-Helices and β-pleated sheets are examples of the tertiary structure of a protein. (18.6)
15. The majority of amino acids in proteins are β-amino acids. (18.2)
16. Proteins can act as catalysts in chemical reactions. (18.1)
17. In electrophoresis, species with a net negative charge will move toward the negative electrode. (18.3)
18. All naturally occurring amino acids are chiral. (18.2)
19. Cyanogen bromide, trypsin, and chymotrypsin each act to cleave peptide bonds at specific amino acids. (18.5)
20. The carboxyl group of an α-amino acid is more acidic than the carboxyl group of an aliphatic carboxylic acid. (18.3)
21. The amino acid sequence of a protein or polypeptide is known as its secondary structure. (18.5)
22. The 20 common, naturally occurring amino acids can be represented by both three- and one-letter abbreviations. (18.2)
23. The side chain of histidine shows enhanced basicity because of the electron-withdrawing inductive effects that stabilize the ion that results after protonation. (18.3)
24. The quaternary structure of a protein describes how smaller, individual protein strands interact to form the overall structure of a protein. (18.6)
25. An amino acid with a net charge of +1 is classified as a zwitterion. (18.2)
26. The side chain in serine is polar and can undergo hydrogen bonding. (18.2)

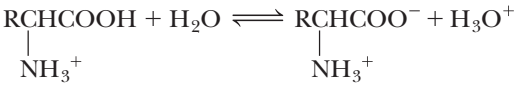
Detailed explanations for many of these answers can be found in the accompanying Solutions Manual.

Answers: (1) F (2) T (3) T (4) T (5) F (6) F (7) F (8) T (9) F (10) F (11) T (12) F (13) T (14) F (15) F (16) T (17) F (18) F (19) T (20) T (21) F (22) T (23) T (24) T (25) F (26) T

KEY REACTIONS

1. Acidity of an α-Carboxyl Group (Section 18.3A)

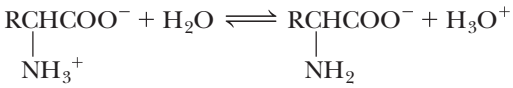
An α-COOH (pK_a approximately 2.19) of a protonated amino acid is a considerably stronger acid than acetic acid (pK_a 4.76) or other low-molecular-weight aliphatic carboxylic acid, due to the electron-withdrawing inductive effect of the α-NH_3^+ group:



pK_a = 2.19

2. Acidity of an α-Ammonium Group (Section 18.3A)

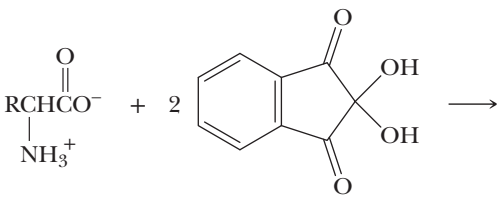
An α-NH_3^+ group (pK_a approximately 9.47) is a slightly stronger acid than a primary aliphatic ammonium ion (pK_a approximately 10.76):



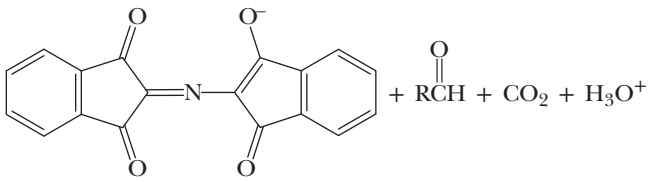
pK_a = 9.47

3. Reaction of an α-Amino Acid with Ninhydrin (Section 18.3D)

Treating an α-amino acid with ninhydrin gives a purple-colored solution:



An α-amino acid — Ninhydrin

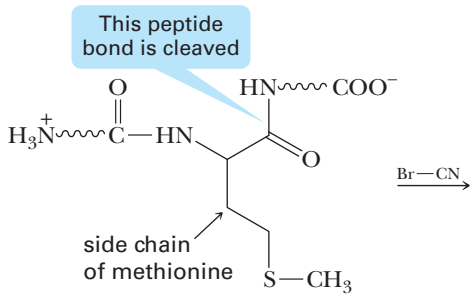


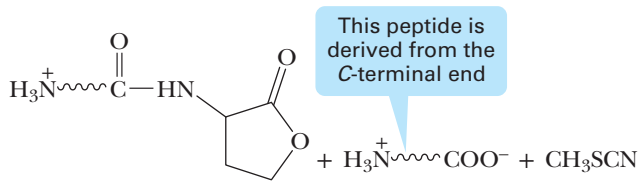
Purple-colored anion

Treating proline with ninhydrin gives an orange-colored solution.

4. Cleavage of a Peptide Bond by Cyanogen Bromide (Section 18.5B)

Cleavage is regioselective for a peptide bond formed by the carboxyl group of methionine:

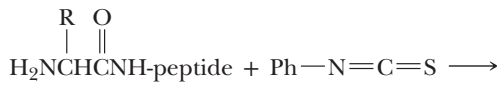




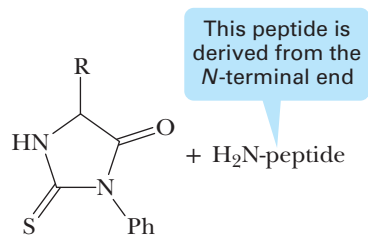
A substituted γ-lactone of the amino acid homoserine

5. Edman Degradation (Section 18.5B)

Treatment with phenyl isothiocyanate followed by acid removes the *N*-terminal amino acid as a substituted phenylthiohydantoin, which is then separated and identified:



Phenylisothiocyanate



A phenylthiohydantoin

PROBLEMS

A problem marked with an asterisk indicates an applied "real-world" problem. Answers to problems whose numbers are printed in blue are given in Appendix D.

SECTION 18.2 Amino Acids

18.8 What amino acid does each abbreviation stand for?

(a) Phe (b) Ser (c) Asp (d) Gln
(e) His (f) Gly (g) Tyr (h) Trp

18.9 The configuration of the stereocenter in α-amino acids is most commonly specified using the D,L convention. The configuration can also be identified using the *R*,*S* convention (Section 6.3). Does the stereocenter in L-serine have the *R* or the *S* configuration?

18.10 Assign an R or S configuration to the stereocenter in each amino acid:

(a) L-Phenylalanine (c) L-Methionine
(b) L-Glutamic acid (d) L-Proline

18.11 The amino acid threonine has two stereocenters. The stereoisomer found in proteins has the configuration 2*S*, 3*R* about the two stereocenters. Draw a Fischer projection of this stereoisomer and also a three-dimensional representation.

18.12 Define the term *zwitterion*.

18.13 Draw zwitterion forms of these amino acids:

(a) Valine (b) Phenylalanine (c) Glutamine (d) Proline

18.14 Why are Glu and Asp often referred to as acidic amino acids? **(See Example 18.1)**

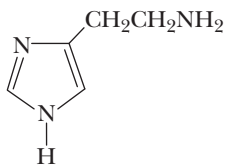
18.15 Why is Arg often referred to as a basic amino acid? Which two other amino acids are also referred to as basic amino acids? **(See Example 18.1)**

18.16 What is the meaning of the alpha as it is used in α-amino acid?

***18.17** Several β-amino acids exist. A unit of β-alanine, for example, is contained within the structure of coenzyme A (Section 21.1D). Write the structural formula of β-alanine.

***18.18** Although only L-amino acids occur in proteins, D-amino acids are often a part of the metabolism of lower organisms. The antibiotic actinomycin D, for example, contains a unit of D-valine, and the antibiotic bacitracin A contains units of D-asparagine and D-glutamic acid. Draw Fischer projections and three-dimensional representations for these three D-amino acids.

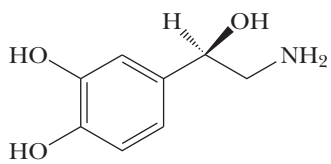
***18.19** Histamine is synthesized from one of the 20 protein-derived amino acids. Suggest which amino acid is the biochemical precursor of histamine, and name the type of organic reaction(s) (e.g., oxidation, reduction, decarboxylation, nucleophilic substitution) involved in its conversion to histamine.



Histamine

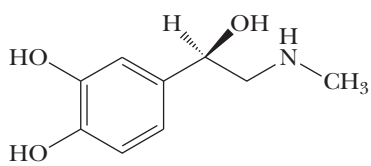
***18.20** Both norepinephrine and epinephrine are synthesized from the same protein-derived amino acid:

(a)



Norepinephrine

(b)

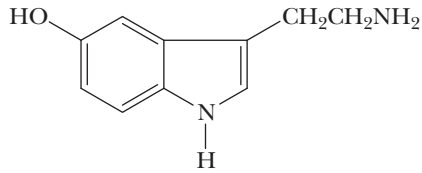


Epinephrine
(Adrenaline)

From which amino acid are the two compounds synthesized, and what types of reactions are involved in their biosynthesis?

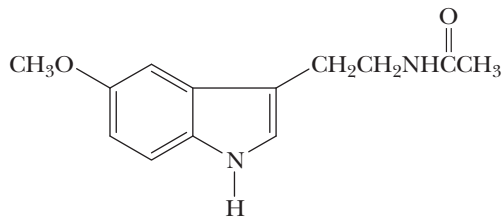
***18.21** From which amino acid are serotonin and melatonin synthesized, and what types of reactions are involved in their biosynthesis?

(a)



Serotonin

(b)



Melatonin

SECTION 18.3 Acid–Base Behavior of Amino Acids

18.22 Draw a structural formula for the form of each amino acid most prevalent at pH 1.0 **(See Example 18.2):**

(a) Threonine (c) Methionine
(b) Arginine (d) Tyrosine

18.23 Draw a structural formula for the form of each amino acid most prevalent at pH 10.0 **(See Example 18.2):**

(a) Leucine (c) Proline
(b) Valine (d) Aspartic acid

18.24 Write the zwitterion form of alanine and show its reaction with:

(a) 1.0 mol NaOH (b) 1.0 mol HCl

18.25 Write the form of lysine most prevalent at pH 1.0, and then show its reaction with each of the following (consult Table 18.2 for pK_a values of the ionizable groups in lysine) **(See Example 18.2):**

(a) 1.0 mol NaOH (b) 2.0 mol NaOH (c) 3.0 mol NaOH

18.26 Write the form of aspartic acid most prevalent at pH 1.0, and then show its reaction with the following (consult Table 18.2 for pK_a values of the ionizable groups in aspartic acid) **(See Example 18.2):**

(a) 1.0 mol NaOH (b) 2.0 mol NaOH (c) 3.0 mol NaOH

18.27 Given pK_a values for ionizable groups from Table 18.2, sketch curves for the titration of (a) glutamic acid with NaOH and (b) histidine with NaOH.

18.28 Draw a structural formula for the product formed when alanine is treated with each of the following reagents:

(a) Aqueous NaOH (b) Aqueous HCl
(c) CH_3CH_2OH, H_2SO_4 (d) $CH_3C(O)Cl$

18.29 Account for the fact that the isoelectric point of glutamine (pI 5.65) is higher than the isoelectric point of glutamic acid (pI 3.08).

18.30 Enzyme-catalyzed decarboxylation of glutamic acid gives 4-aminobutanoic acid (Section 18.2D). Estimate the pI of 4-aminobutanoic acid.

18.31 Guanidine and the guanidino group present in arginine are two of the strongest organic bases known. Account for their basicity.

***18.32** At pH 7.4, the pH of blood plasma, do the majority of protein-derived amino acids bear a net negative charge or a net positive charge? **(See Example 18.2)**

18.33 Do the following compounds migrate to the cathode or the anode on electrophoresis at the specified pH? **(See Example 18.2)**

(a) Histidine at pH 6.8
(b) Lysine at pH 6.8
(c) Glutamic acid at pH 4.0
(d) Glutamine at pH 4.0
(e) Glu-Ile-Val at pH 6.0
(f) Lys-Gln-Tyr at pH 6.0

18.34 At what pH would you carry out an electrophoresis to separate the amino acids in each of the following mixtures? **(See Example 18.3)**

(a) Ala, His, Lys (b) Glu, Gln, Asp (c) Lys, Leu, Tyr

***18.35** Examine the amino acid sequence of human insulin (Figure 18.13), and list each Asp, Glu, His, Lys, and Arg in this molecule. Do you expect human insulin to have an isoelectric point nearer that of the acidic amino acids (pI 2.0–3.0), the neutral amino acids (pI 5.5–6.5), or the basic amino acids (pI 9.5–11.0)?

SECTION 18.5 Primary Structure of Polypeptides and Proteins

18.36 If a protein contains four different SH groups, how many different disulfide bonds are possible if only a single disulfide bond is formed? How many different disulfides are possible if two disulfide bonds are formed?

18.37 How many different tetrapeptides can be made if **(See Example 18.4)**

(a) The tetrapeptide contains one unit each of Asp, Glu, Pro, and Phe?
(b) All 20 amino acids can be used, but each only once?

18.38 A decapeptide has the following amino acid composition: **(See Example 18.6)**

Ala_2, Arg, Cys, Glu, Gly, Leu, Lys, Phe, Val

Partial hydrolysis yields the following tripeptides:

Cys-Glu-Leu + Gly-Arg-Cys + Leu-Ala-Ala +
Lys-Val-Phe + Val-Phe-Gly

One round of Edman degradation yields a lysine phenylthiohydantoin. From this information, deduce the primary structure of the given decapeptide.

***18.39** Following is the primary structure of glucagon, a polypeptide hormone with 29 amino acids: **(See Example 18.5)**

1 5 10
His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-
15 20 25
Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-
29
Leu-Met-Asn-Thr

Glucagon

Glucagon is produced in the α-cells of the pancreas and helps maintain the blood glucose concentration within a normal range. Which peptide bonds are hydrolyzed when glucagon is treated with each reagent?

(a) Phenyl isothiocyanate
(b) Chymotrypsin
(c) Trypsin
(d) Br-CN

18.40 A tetradecapeptide (14 amino acid residues) gives the following peptide fragments on partial hydrolysis **(See Example 18.6)**:

Pentapeptide Fragments	Tetrapeptide Fragments
Phe-Val-Asn-Gln-His	Gln-His-Leu-Cys
His-Leu-Cys-Gly-Ser	His-Leu-Val-Glu
Gly-Ser-His-Leu-Val	Leu-Val-Glu-Ala

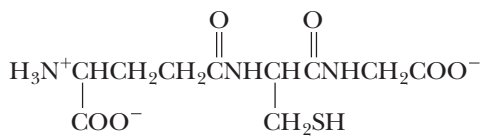
From the information shown, deduce the primary structure of the given polypeptide. Fragments are grouped according to size.

18.41 Draw a structural formula of each of the following tripeptides: marking each peptide bond, the *N*-terminal amino acid, and the *C*-terminal amino acid: **(See Example 18.4)**

(a) Phe-Val-Asn (b) Leu-Val-Gln

18.42 Estimate the pI of each tripeptide in Problem 18.41.

***18.43** Glutathione (G-SH), one of the most common tripeptides in animals, plants, and bacteria, is a scavenger of oxidizing agents:

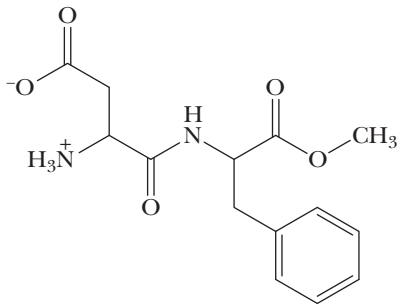
Glutathione 

In reacting with oxidizing agents, glutathione is converted to G-S-S-G.

(a) Name the amino acids in this tripeptide.
(b) What is unusual about the peptide bond formed by the *N*-terminal amino acid?
(c) Is glutathione a biological oxidizing agent or a biological reducing agent?
(d) Write a balanced equation for the reaction of glutathione with molecular oxygen, O_2, to form G-S-S-G and H_2O. Is molecular oxygen oxidized or reduced in this reaction?

***18.44** Following is a structural formula for the artificial sweetener aspartame:

(a) Name the two amino acids in this molecule.
(b) Estimate the isoelectric point of aspartame.
(c) Draw structural formulas for the products of the hydrolysis of aspartame in 1 M HCl.



Aspartame

SECTION 18.6 Three-Dimensional Shapes of Polypeptides and Proteins

18.45 Examine the α-helix conformation. Are amino acid side chains arranged all inside the helix, all outside the helix, or randomly?

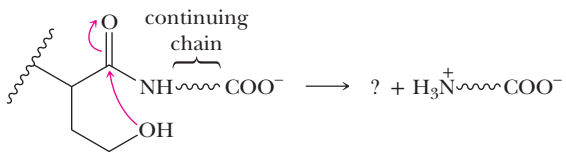
18.46 Distinguish between intermolecular and intramolecular hydrogen bonding between the backbone groups on polypeptide chains. In what type of secondary structure do you find intermolecular hydrogen bonds? In what type do you find intramolecular hydrogen bonding?

***18.47** Many plasma proteins found in an aqueous environment are globular in shape. Which of the following amino acid side chains would you expect to find on the surface of a globular protein, in contact with the aqueous environment, and which would you expect to find inside, shielded from the aqueous environment? Explain. **(See Example 18.7)**

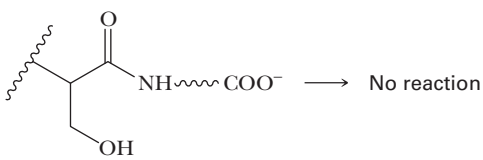
(a) Leu (b) Arg (c) Ser (d) Lys (e) Phe

LOOKING AHEAD

18.48 Some amino acids cannot be incorporated into proteins because they are self-destructive. Homoserine, for example, can use its side-chain OH group in an intramolecular nucleophilic acyl substitution to cleave the peptide bond and form a cyclic structure on one end of the chain:



Homoserine residue

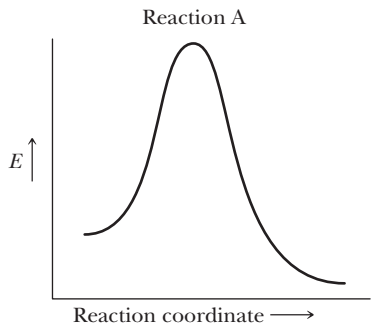


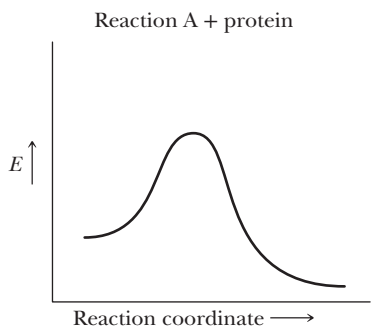
Serine residue

Draw the cyclic structure formed and explain why serine does not suffer the same fate.

18.49 Would you expect a decapeptide of only isoleucine residues to form an α-helix? Explain.

18.50 Which type of protein would you expect to bring about the following change?





GROUP LEARNING ACTIVITIES

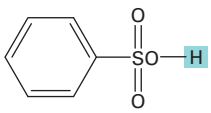
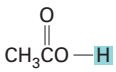
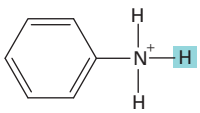
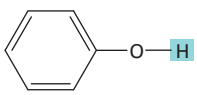
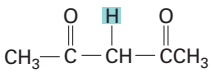
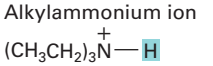
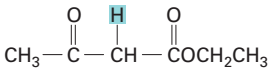
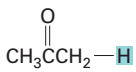
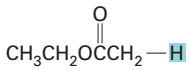
18.51 Heating can disrupt the 2° and 3° structure of a protein. Apply what you know about intermolecular forces and discuss the chemical processes that could occur upon heating a protein.

18.52 Enzymes are examples of proteins. Discuss why enzymes lose their catalytic activity at higher than physiological temperatures.

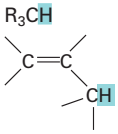
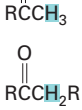
18.53 Denaturation is the loss of secondary, tertiary, and quaternary structure of a protein by a chemical or physical agent and the resulting loss of function. The previous two problems revealed that heat can cause denaturation. As a group, discuss other physical or chemical agents that could cause denaturation and explain the processes that would effect denaturation.

You'll find Chapter 19, Lipids, Chapter 20, Nucleic Acids, and Chapter 21, The Organic Chemistry of Metabolism, online at www.wiley.com/college/brown and in WileyPLUS.

Acid Ionization Constants for the Major Classes of Organic Acids

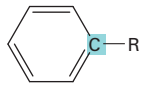
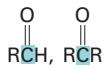
Class and Example	Typical pK_a
Sulfonic acid 	(–3)–(–2)
Carboxylic acid 	3–5
Arylammonium ion 	4–5
Thiol $CH_3CH_2S—H$	8–12
Phenol 	9–10
β-Diketone 	10
Alkylammonium ion 	10–12
β-Ketoester 	11
Water $HO—H$	15.7
Alcohol $CH_3CH_2O—H$	15–19
α-Hydrogen of an aldehyde or ketone 	18–20
α-Hydrogen of an ester 	23–25
Terminal alkyne $CH_3—C\equiv C—H$	25
Aliphatic amine $(CH_3CH_2)_2N—H$	36
Allylic hydrogen of an alkene $CH_2=CHCH_2—H$	43
Alkene $CH_2=CH—H$	50
Alkane $(CH_3)_2CH—H$	>51

Characteristic ^{1}H-NMR Chemical Shifts

Type of Hydrogen (R = alkyl, Ar = aryl)	Chemical Shift (δ)*
$(CH_3)_4Si$	0 (by definition)
RCH_3	0.8–1.0
RCH_2R	1.2–1.4
R_3CH	1.4–1.7
	1.6–2.6
$RC\equiv CH$	2.0–3.0
$ArCH_3$	2.2–2.5
$ArCH_2R$	2.3–2.8
ROH	0.5–6.0
RCH_2OH	3.4–4.0
RCH_2OR	3.3–4.0
R_2NH	0.5–5.0
	2.1–2.3
	2.2–2.6
	3.7–3.9
	4.1–4.7
RCH_2I	3.1–3.3
RCH_2Br	3.4–3.6
RCH_2Cl	3.6–3.8
RCH_2F	4.4–4.5
$ArOH$	4.5–4.7
$R_2C=CH_2$	4.6–5.0
$R_2C=CHR$	5.0–5.7
ArH	6.5–8.5
	9.5–10.1
	10–13

*Values are relative to tetramethylsilane. Other atoms within the molecule may cause the signal to appear outside these ranges.

Characteristic ^{13}C-NMR Chemical Shifts

Type of Carbon	Chemical Shift (δ)	Type of Carbon	Chemical Shift (δ)
RCH_3	0–40		110–160
RCH_2R	15–55		160–180
R_3CH	20–60		165–180
RCH_2I	0–40		175–185
RCH_2Br	25–65		180–210
RCH_2Cl	35–80		
R_3COH	40–80		
R_3COR	40–80		
$RC{\equiv}CR$	65–85		
$R_2C{=}CR_2$	100–150		

Characteristic Infrared Absorption Frequencies

Bonding	Functional Group	Frequency (cm^{-1})	Intensity*
C—H	alkane	2850–3000	w–m
	—CH_3	1375 and 1450	w–m
	—CH_2—	1450	m
	alkene	3000–3100	w–m
		650–1000	s
	alkyne	3270–3330	w–m
		1600–1680	w–m
	aromatic	3000–3100	s
		690–900	s
	aldehyde	2700–2800	w
		2800–2900	w
C=C	alkene	1600–1680	w–m
	aromatic	1450 and 1600	w–m
C—O	alcohol, ether,	1050–1100 (sp^3 C—O)	s
	ester, carboxylic		s
	acid, anhydride	1200–1250 (sp^2 C—O)	s
C=O	amide	1630–1680	s
	carboxylic acid	1700–1725	s
	ketone	1705–1780	s
	aldehyde	1705–1740	s
	ester	1735–1800	s
	anhydride	1760 and 1800	s
O—H	alcohol, phenol		
	free	3600–3650	m
	H-bonded	3200–3500	m
	carboxylic acid	2400–3400	m
N—H	amine and amide	3100–3500	m–s

*w = weak, m = medium, s = strong

Acetal A molecule containing two —OR or —OAr groups bonded to the same carbon.
Aceto group A group.
Achiral An object that lacks chirality; an object that has no handedness and is superposable on its mirror image.
Acid halide A derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen—most commonly, chlorine.
Activating group Any substituent on a benzene ring that causes the rate of electrophilic aromatic substitution to be greater than that for benzene.
Activation energy, E_a The difference in energy between reactants and the transition state.
Active metal A metal that readily loses an electron to form a cation.
Acyl halide A derivative of a carboxylic acid in which the —OH of the carboxyl group is replaced by a halogen—most commonly, chlorine.
Alcohol A compound containing an —OH (hydroxyl) group bonded to an sp^3 hybridized carbon.
Alcoholic fermentation A metabolic pathway that converts glucose to two molecules of ethanol and two molecules of CO_2.
Aldehyde A compound containing a carbonyl group bonded to hydrogen (a —CHO group).
Alditol The product formed when the C═O group of a monosaccharide is reduced to a CHOH group.
Aldol reaction A carbonyl condensation reaction between two aldehydes or ketones to give a *β*-hydroxyaldehyde or a *β*-hydroxyketone.
Aldose A monosaccharide containing an aldehyde group.
Aliphatic amine An amine in which nitrogen is bonded only to alkyl groups.
Alkane A saturated hydrocarbon whose carbon atoms are arranged in an open chain.
Alkene An unsaturated hydrocarbon that contains a carbon–carbon double bond.
Alkoxy group An —OR group, where R is an alkyl group.
Alkyl group A group derived by removing a hydrogen from an alkane; given the symbol R–.
Alkyne An unsaturated hydrocarbon that contains a carbon–carbon triple bond.
α-Amino acid An amino acid in which the amino group is on the carbon adjacent to the carboxyl group.
Amino acid A compound that contains both an amino group and a carboxyl group.
Amino group An sp^3 hybridized nitrogen atom bonded to one, two, or three carbon groups.
Amorphous domains Disordered, noncrystalline regions in the solid state of a polymer.
Anabolic steroid A steroid hormone, such as testosterone, that promotes tissue and muscle growth and development.
Androgen A steroid hormone, such as testosterone, that mediates the development and sexual characteristics of males.
Angle strain The strain that arises when a bond angle is either compressed or expanded compared with its optimal value.
Anion An atom or group of atoms bearing a negative charge.
Anomeric carbon The hemiacetal carbon of the cyclic form of a monosaccharide.
Anomers Monosaccharides that differ in configuration only at their anomeric carbons.
Anti stereoselectivity Addition of atoms or groups of atoms from opposite sides or faces of a carbon–carbon double bond.
Aprotic solvents A solvent that cannot serve as a hydrogen bond donor as, for example, acetone, diethyl ether, and dichloromethane.
Ar— The symbol used for an aryl group, by analogy with R— for an alkyl group.
Aramid A polyaromatic *amide*; a polymer in which the monomer units are an aromatic diamine and an aromatic dicarboxylic acid.
Arene A compound containing one or more benzene rings. An aromatic hydrocarbon.
Aromatic amine An amine in which nitrogen is bonded to one or more aryl groups.
Aromatic compound A term used to classify benzene and its derivatives.
Arrhenius acid A substance that dissolves in water to produce H^+ ions.
Arrhenius base A substance that dissolves in water to produce OH^- ions.
Aryl group A group derived from an aromatic compound (an arene) by the removal of an H; given the symbol Ar—.
Autoclave An instrument used to sterilize items by subjecting them to steam and high pressure.
Average degree of polymerization, (*n*) A subscript placed outside the parentheses of the simplest nonredundant unit of a polymer to indicate that the unit repeats *n* times in the polymer.
Axial bond A bond on a chair conformation of a cyclohexane ring that extends from the ring parallel to the imaginary axis of the ring.
Benzyl group $C_6H_5CH_2$—, the alkyl group derived by removing a hydrogen from the methyl group of toluene.
Benzylic carbon An sp^3 hybridized carbon bonded to a benzene ring.
Bile acid A cholesterol-derived detergent molecule, such as cholic acid, that is secreted by the gallbladder into the intestine to assist in the absorption of dietary lipids.
Bimolecular reaction A reaction in which two species are involved in the reaction leading to the transition state of the rate-determining step.
Boat conformation A puckered conformation of a cyclohexane ring in which carbons 1 and 4 of the ring are bent toward each other.
Bonding electrons Valence electrons shared in a covalent bond.
Brønsted–Lowry acid A proton donor.
Brønsted–Lowry base A proton acceptor.
Carbanion An anion in which carbon has an unshared pair of electrons and bears a negative charge.
Carbocation A species containing a carbon atom with only three bonds to it and bearing a positive charge.
Carbohydrate A polyhydroxyaldehyde or polyhydroxyketone or a substance that gives these compounds on hydrolysis.
Carbonyl group A C═O group.
Carboxyl group A —COOH group.
Carboxylic anhydride A compound in which two acyl groups are bonded to an oxygen.
Cation An atom or group of atoms bearing a positive charge.
Chain initiation In radical polymerization, the formation of radicals from molecules containing only paired electrons.
Chain propagation In radical polymerization, a reaction of a radical and a molecule to give a new radical.
Chain termination In radical polymerization, a reaction in which two radicals combine to form a covalent bond.
Chain-growth polymerization A polymerization that involves sequential addition reactions, either to unsaturated monomers or to monomers possessing other reactive functional groups.
Chain-transfer reaction In radical polymerization, the transfer of reactivity of an end group from one chain to another during a polymerization.
Chair conformation The most stable puckered conformation of a cyclohexane ring; all bond angles are approximately 109.5°, and bonds to all adjacent carbons are staggered.
Chemical shift (δ) The position of a signal on an NMR spectrum relative to the signal of tetramethylsilane (TMS); expressed in delta (δ) units, where one δ equals 1 ppm.
Chiral From the Greek *cheir*, meaning hand; chiral objects are not superposable on their mirror images.
Chiral center An atom, most commonly a carbon, with four different groups bonded to it.
Chromatin A complex formed between negatively charged DNA molecules and positively charged histones.
Circular DNA A type of double-stranded DNA in which the 5′ and 3′ ends of each strand are joined by phosphodiester groups.
Cis A prefix meaning "on the same side."
***Cis–trans* isomers** Isomers that have the same order of attachment (connectivity) of their atoms, but a different arrangement of their atoms in space due to the presence of either a ring (Chapter 3) or a carbon–carbon double bond (Chapter 4).

Claisen condensation A carbonyl condensation reaction between two esters to give a β-ketoester.

Codon A triplet of nucleotides on mRNA that directs the incorporation of a specific amino acid into a polypeptide sequence.

Coenzyme A low-molecular-weight, nonprotein molecule or ion that binds reversibly to an enzyme, functions as a second substrate for the enzyme, and is regenerated by further reaction.

Conformation Any three-dimensional arrangement of atoms in a molecule that results by rotation about a single bond.

Conjugate acid The species formed when a base accepts a proton.

Conjugate base The species formed when an acid donates a proton.

Constitutional isomers Compounds with the same molecular formula, but a different order of attachment (connectivity) of their atoms.

Covalent bond A chemical bond resulting from the sharing of one or more pairs of electrons.

Crossed aldol reaction An aldol reaction between two different aldehydes, two different ketones, or an aldehyde and a ketone.

Crossed Claisen condensation A Claisen condensation between two different esters.

Crystalline domains Ordered crystalline regions in the solid state of a polymer; also called crystallites.

C-Terminal amino acid The amino acid at the end of a polypeptide chain having the free —COO^- group.

Curved arrow A symbol used to show the redistribution of valence electrons.

Cyclic ethers An ether in which the oxygen is one of the atoms of a ring.

Cycloalkane A saturated hydrocarbon that contains carbon atoms joined to form a ring.

Deactivating group Any substituent on a benzene ring that causes the rate of electrophilic aromatic substitution to be lower than that for benzene.

Decarboxylation Loss of CO_2 from a carboxyl group.

Dehydration Elimination of a molecule of water from a compound.

Dehydrohalogenation Removal of —H and —X from adjacent carbons; a type of β-elimination.

Dextrorotatory Rotating the plane of polarized light in a polarimeter to the right.

Diastereomers Stereoisomers that are not mirror images of each other; the term refers to relationships among objects.

Diaxial interactions Interactions between groups in parallel axial positions on the same side of a chair conformation of a cyclohexane ring.

Dieckmann condensation An intramolecular Claisen condensation of an ester of a dicarboxylic acid to give a five- or six-membered ring.

Dipeptide A molecule containing two amino acid units joined by a peptide bond.

Disaccharide A carbohydrate containing two monosaccharide units joined by a glycosidic bond.

Dispersion forces Very weak intermolecular forces of attraction resulting from the interaction of temporary induced dipoles.

Disulfide bond A covalent bond between two sulfur atoms; an —S—S— bond.

D-Monosaccharide A monosaccharide that, when written as a Fischer projection, has the —OH on its penultimate carbon to the right.

Double helix A type of secondary structure of DNA molecules in which two antiparallel polynucleotide strands are coiled in a right-handed manner about the same axis.

Double-headed arrows A symbol used to connect contributing structures.

Doublet A signal that is split into two peaks; the hydrogens that give rise to the signal have one neighboring nonequivalent hydrogen.

Downfield A term used to refer to the relative position of a signal on an NMR spectrum. Downfield indicates a peak to the left of the spectrum (a weaker applied field).

E From the German *entgegen*, meaning opposite; specifies that groups of higher priority on the carbons of a double bond are on opposite sides.

Eclipsed conformation A conformation about a carbon–carbon single bond in which the atoms on one carbon are as close as possible to the atoms on the adjacent carbon.

Edman degradation A method for selectively cleaving and identifying the *N*-terminal amino acid of a polypeptide chain.

***β*-elimination** The removal of atoms or groups of atoms from two adjacent carbon atoms, as for example, the removal of H and X from an alkyl halide or H and OH from an alcohol to form a carbon–carbon double bond.

Elastomer A material that, when stretched or otherwise distorted, returns to its original shape when the distorting force is released.

Electromagnetic radiation Light and other forms of radiant energy.

Electronegativity A measure of the force of an atom's attraction for electrons it shares in a chemical bond with another atom.

Electrophile An electron-poor species that can accept a pair of electrons to form a new covalent bond; alternatively, a Lewis acid (Section 2.6).

Electrophilic aromatic substitution A reaction in which an electrophile, E^+, substitutes for a hydrogen on an aromatic ring.

Electrophoresis The process of separating compounds on the basis of their electric charge.

Enantiomers Stereoisomers that are nonsuperposable mirror images; the term refers to a relationship between pairs of objects.

5' End The end of a polynucleotide at which the 5′-OH of the terminal pentose unit is free.

Endothermic reaction A reaction in which the energy of the products is higher than the energy of the reactants; a reaction in which heat is absorbed.

3' End The end of a polynucleotide at which the 3′-OH of the terminal pentose unit is free.

Energy diagram A graph showing the changes in energy that occur during a chemical reaction; energy is plotted on the *y*-axis, and the progress of the reaction is plotted on the *x*-axis.

Enol A molecule containing an —OH group bonded to a carbon of a carbon–carbon double bond.

Enolate anion An anion formed by the removal of an α-hydrogen from a carbonyl-containing compound.

Epoxide A cyclic ether in which oxygen is one atom of a three-membered ring.

Epoxy resin A material prepared by a polymerization in which one monomer contains at least two epoxy groups.

Equatorial bond A bond on a chair conformation of a cyclohexane ring that extends from the ring roughly perpendicular to the imaginary axis of the ring.

Equivalent hydrogens Hydrogens that have the same chemical environment.

Estrogen A steroid hormone, such as estradiol, that mediates the development and sexual characteristics of females.

Ether A compound containing an oxygen atom bonded to two carbon atoms.

Exothermic reaction A reaction in which the energy of the products is lower than the energy of the reactants; a reaction in which heat is liberated.

***E,Z* system** A system used to specify the configuration of groups about a carbon–carbon double bond.

Fat A triglyceride that is semisolid or solid at room temperature.

Fatty acids A long, unbranched-chain carboxylic acid, most commonly of 12 to 20 carbons, derived from the hydrolysis of animal fats, vegetable oils, or the phospholipids of biological membranes.

Fingerprint region The portion of the vibrational infrared region that extends from 1000 to 400 cm^{-1} and that is unique to every compound.

Fischer esterification The process of forming an ester by refluxing a carboxylic acid and an alcohol in the presence of an acid catalyst, commonly sulfuric acid.

Fischer projection A two-dimensional representation showing the configuration of a stereocenter; horizontal lines represent bonds projecting forward from the stereocenter, whereas vertical lines represent bonds projecting to the rear. The stereocenter is the only atom in the plane.

Fishhook arrow A single-barbed, curved arrow used to show the change in position of a single electron.

Flavin adenine dinucleotide (FAD) A biological oxidizing agent. When acting as an oxidizing agent, FAD is reduced to $FADH_2$.

Fluid-mosaic model A model of a biological membrane consisting of a phospholipid bilayer, with proteins, carbohydrates, and other lipids embedded in, and on the surface of, the bilayer.

Formal charge The charge on an atom in a molecule or polyatomic ion.

Frequency (ν) A number of full cycles of a wave that pass a point in a second.

Functional group An atom or a group of atoms within a molecule that shows a characteristic set of physical and chemical properties.

Furanose A five-membered cyclic hemiacetal form of a monosaccharide.

Glycols A compound with two hydroxyl (—OH) groups on different carbons.

Glycolysis From the Greek *glyko*, sweet, and *lysis*, splitting; a series of ten enzyme-catalyzed reactions by which glucose is oxidized to two molecules of pyruvate.

Glycoside A carbohydrate in which the —OH on its anomeric carbon is replaced by —OR.

Glycosidic bond The bond from the anomeric carbon of a glycoside to an —OR group.

Grignard reagent An organomagnesium compound of the type RMgX or ArMgX.

Ground-state electron configuration The electron configuration of lowest energy for an atom, molecule, or ion.

Haloalkane (alkyl halide) A compound containing a halogen atom covalently bonded to an sp^3 hybridized carbon atom; given the symbol RX.

Halonium ion An ion in which a halogen atom bears a positive charge.

Haworth projection A way of viewing the furanose and pyranose forms of monosaccharides. The ring is drawn flat and viewed through its edge, with the anomeric carbon on the right and the oxygen atom of the ring in the rear to the right.

Heat of reaction, ΔH The difference in energy between reactants and products.

Hemiacetal A molecule containing an —OH and an —OR or —OAr group bonded to the same carbon.

α-Helix A type of secondary structure in which a section of polypeptide chain coils into a spiral, most commonly a right-handed spiral.

Hertz The unit in which wave frequency is reported; s^{-1} (read *per second*).

Heterocyclic amine An amine in which nitrogen is one of the atoms of a ring.

Heterocyclic aromatic amine An amine in which nitrogen is one of the atoms of an aromatic ring.

Heterocyclic compounds An organic compound that contains one or more atoms other than carbon in its ring.

High-density lipoprotein (HDL) Plasma particles, of density 1.06–1.21 g/mL, consisting of approximately 33% proteins, 30% cholesterol, 29% phospholipids, and 8% triglycerides.

Histone A protein, particularly rich in the basic amino acids lysine and arginine, that is found associated with DNA molecules.

Hybrid orbitals An orbital produced from the combination of two or more atomic orbitals.

Hydration Addition of water.

Hydride ion A hydrogen atom with two electrons in its valence shell; $H:^-$.

Hydrocarbon A compound that contains only carbon atoms and hydrogen atoms.

Hydrogen bonding The attractive force between a partial positive charge on hydrogen and partial negative charge on a nearby oxygen, nitrogen, or fluorine atom.

Hydrophilic From the Greek, meaning "water loving."

Hydrophobic From the Greek, meaning "water hating."

Hydrophobic effect The tendency of nonpolar groups to cluster in such a way as to be shielded from contact with an aqueous environment.

Hydroxyl group An —OH group.

α-Carbon A carbon atom adjacent to a carbonyl group.

α-Hydrogen A hydrogen on an α-carbon.

Imine A compound containing a carbon–nitrogen double bond; also called a Schiff base.

Index of hydrogen deficiency (IHD) The sum of the number of rings and pi bonds in a molecule.

Inductive effect The polarization of electron density transmitted through covalent bonds caused by a nearby atom of higher electronegativity.

Inversion of configuration The reversal of the arrangement of atoms or groups of atoms about a reaction center in an S_N2 reaction.

Ionic bond A chemical bond resulting from the electrostatic attraction of an anion and a cation.

Isoelectric point (pI) The pH at which an amino acid, a polypeptide, or a protein has no net charge.

Ketone A compound containing a carbonyl group bonded to two carbons.

Ketose A monosaccharide containing a ketone group.

Lactam A cyclic amide.

Lactate fermentation A metabolic pathway that converts glucose to two molecules of lactate.

Lactone A cyclic ester.

Levorotatory Rotating the plane of polarized light in a polarimeter to the left.

Lewis acid Any molecule or ion that can form a new covalent bond by accepting a pair of electrons.

Lewis base Any molecule or ion that can form a new covalent bond by donating a pair of electrons.

Lewis structure of an atom The symbol of an element surrounded by a number of dots equal to the number of electrons in the valence shell of the atom.

Line-angle formula An abbreviated way to draw structural formulas in which each vertex and each line ending represents a carbon atom and a line represents a bond.

Lipid A heterogeneous class of compounds grouped together on the basis of their solubility properties; they are insoluble in water and soluble in diethyl ether, acetone, and dichloromethane. Carbohydrates, amino acids, and proteins are largely insoluble in these organic solvents.

Lipid bilayer A back-to-back arrangement of phospholipid monolayers.

L-Monosaccharide A monosaccharide that, when written as a Fischer projection, has the —OH on its penultimate carbon to the left.

Low-density lipoprotein (LDL) Plasma particles, of density 1.02–1.06 g/mL, consisting of approximately 25% proteins, 50% cholesterol, 21% phospholipids, and 4% triglycerides.

Markovnikov's rule In the addition of HX or H_2O to an alkene, hydrogen adds to the carbon of the double bond having the greater number of hydrogens.

Mercaptan A common name for any molecule containing an —SH group.

Meso compound An achiral compound possessing two or more stereocenters.

Messenger RNA (mRNA) A ribonucleic acid that carries coded genetic information from DNA to ribosomes for the synthesis of proteins.

Meta (m) Refers to groups occupying positions 1 and 3 on a benzene ring.

Meta directing Any substituent on a benzene ring that directs electrophilic aromatic substitution preferentially to a meta position.

Micelle A spherical arrangement of organic molecules in water solution clustered so that their hydrophobic parts are buried inside the sphere and their hydrophilic parts are on the surface of the sphere and in contact with water.

Michael reaction An anion formed by the removal an enolate anion or other nucleophile to an α,β-unsaturated carbonyl compound.

Mirror image The reflection of an object in a mirror.

Molecular spectroscopy The study of the frequencies of electromagnetic radiation that are absorbed or emitted by substances and the correlation between these frequencies and specific types of molecular structure.

Monomer From the Greek *mono*, single and *meros*, part; the simplest nonredundant unit from which a polymer is synthesized.

Monosaccharide A carbohydrate that cannot be hydrolyzed to a simpler compound.

Multiplet A signal that is split into multiple peaks, often of an irregular pattern, due to the presence of more than one type of neighboring hydrogens.

Mutarotation The change in optical activity that occurs when an α or β form of a carbohydrate is converted to an equilibrium mixture of the two forms.

(n + 1) rule The ^{1}H-NMR signal of a hydrogen or set of equivalent hydrogens with n other hydrogens on neighboring carbons is split into $(n + 1)$ peaks.

Newman projection A way to view a molecule by looking along a carbon–carbon bond.

Nicotinamide adenine dinucleotide (NAD+) A biological oxidizing agent. When acting as an oxidizing agent, NAD^+ is reduced to NADH.

Nomenclature A set of rules for naming organic compounds.

Nonbonding electrons Valence electrons not involved in forming covalent bonds, that is, unshared electrons.

Nonpolar covalent bond A covalent bond between atoms whose difference in electronegativity is less than approximately 0.5.

Nonsuperposable Not able to be overlapped onto another object such that all features match exactly.

Nucleic acid A biopolymer containing three types of monomer units: heterocyclic aromatic amine bases derived from purine and pyrimidine, the monosaccharides D-ribose or 2-deoxy-D-ribose, and phosphate.

Nucleophile An electron-rich atom or group of atoms that can donate a pair of electrons to form a new covalent bond; alternatively, a Lewis base (Section 2.6).

Nucleophilic acyl substitution A reaction in which a nucleophile bonded to a carbonyl carbon is replaced by another nucleophile.

Nucleophilic substitution A reaction in which one nucleophile is substituted for another.

Nucleoside A building block of nucleic acids, consisting of D-ribose or 2-deoxy-D-ribose bonded to a heterocyclic aromatic amine base by a β-*N*-glycosidic bond.

Nucleotide A nucleoside in which a molecule of phosphoric acid is esterified with an —OH of the monosaccharide, most commonly either the 3′-OH or the 5′-OH.

Observed rotation The number of degrees through which a compound rotates the plane of polarized light.

Octet rule The tendency among atoms of Group 1A–7A elements to react in ways that achieve an outer shell of eight valence electrons.

Oil A triglyceride that is liquid at room temperature.

Oligosaccharide A carbohydrate containing from 6 to 10 monosaccharide units, each joined to the next by a glycosidic bond.

Optically active Showing that a compound rotates the plane of polarized light.

Optically inactive Showing that a compound or mixture of compounds does not rotate the plane of polarized light.

Schiff base An alternative name for an imine.

Orbital A region of space where an electron or pair of electrons spends 90 to 95% of its time.

Order of precedence of functional groups A system for ranking functional groups in order of priority for the purposes of IUPAC nomenclature.

Organic chemistry The study of the chemical and physical properties of the compounds of carbon.

Organometallic compound A compound containing a carbon–metal bond.

Ortho (o) Refers to groups occupying positions 1 and 2 on a benzene ring.

Ortho–para directing Any substituent on a benzene ring that directs electrophilic aromatic substitution preferentially to ortho and para positions.

Oxonium ion An ion that contains an oxygen atom bonded to three other atoms or groups of atoms and bears a positive charge.

***β*-Oxidation of fatty acids** A series of four enzyme-catalyzed reactions that cleaves carbon atoms, two at a time, from the carboxyl end of a fatty acid.

Para (p) Refers to groups occupying positions 1 and 4 on a benzene ring.

Peaks (NMR) The units into which an NMR signal is split—two peaks in a doublet, three peaks in a triplet, and so on.

Penultimate carbon The stereocenter of a monosaccharide farthest from the carbonyl group—for example, carbon 5 of glucose.

Peptide bond The special name given to the amide bond formed between the α-amino group of one amino acid and the α-carboxyl group of another amino acid.

Phenol A compound that contains an —OH group bonded to a benzene ring.

Phenyl group C_6H_5—, the aryl group derived by removing a hydrogen from benzene.

Phospholipid A lipid containing glycerol esterified with two molecules of fatty acid and one molecule of phosphoric acid.

pi (π) bond A covalent bond formed by the overlap of parallel *p* orbitals.

***β*-Pleated sheet** A type of secondary structure in which two sections of polypeptide chain are aligned parallel or antiparallel to one another.

Plane of symmetry An imaginary plane passing through an object and dividing it such that one half is the mirror image of the other half.

Plane polarized light Light vibrating only in parallel planes.

Plastic A polymer that can be molded when hot and retains its shape when cooled.

Polar covalent bond A covalent bond between atoms whose difference in electronegativity is between approximately 0.5 and 1.9.

Polarimeter An instrument for measuring the ability of a compound to rotate the plane of polarized light.

Polyamide A polymer in which each monomer unit is joined to the next by an amide bond, as for example Nylon 66.

Polycarbonate A polyester in which the carboxyl groups are derived from carbonic acid.

Polyester A polymer in which each monomer unit is joined to the next by an ester bond as, for example, poly(ethylene terephthalate).

Polymer From the Greek *poly*, many and *meros*, parts; any long-chain molecule synthesized by linking together many single parts called monomers.

Polynuclear aromatic hydrocarbons A hydrocarbon containing two or more fused aromatic rings.

Polypeptide A macromolecule containing 20 or more amino acid units, each joined to the next by a peptide bond.

Polysaccharide A carbohydrate containing a large number of monosaccharide units, each joined to the next by one or more glycosidic bonds.

Polyunsaturated triglyceride A triglyceride having several carbon–carbon double bonds in the hydrocarbon chains of its three fatty acids.

Polyurethane A polymer containing the —NHCOO— group as a repeating unit.

Primary (1°) structure of proteins The sequence of amino acids in the polypeptide chain; read from the *N*-terminal amino acid to the *C*-terminal amino acid.

Primary structure of nucleic acids The sequence of bases along the pentose–phosphodiester backbone of a DNA or RNA molecule, read from the 5′end to the 3′end.

Prostaglandin A member of the family of compounds having the 20-carbon skeleton of prostanoic acid.

Protic solvent A hydrogen bond donor solvent as, for example, water, ethanol, and acetic acid. We define hydrogen bond donors as compounds containing hydrogens that can participate in H-bonding.

Pyranose A six-membered cyclic hemiacetal form of a monosaccharide.

Quaternary (4°) structure of proteins The arrangement of polypeptide monomers into a noncovalently bonded aggregation.

Quartet A signal that is split into four peaks; the hydrogens that give rise to the signal have three neighboring nonequivalent hydrogens that are equivalent to each other.

R From the Latin *rectus*, meaning right; used in the *R,S* system to show that the order of priority of groups on a stereocenter is clockwise.

***R*–** A symbol used to represent an alkyl group.

Racemic mixture A mixture of equal amounts of two enantiomers.

Racemization The conversion of a pure enantiomer into a racemic mixture.

Radical Any molecule that contains one or more unpaired electrons.

Rate-determining step The step in a reaction sequence that crosses the highest energy barrier; the slowest step in a multistep reaction.

Reaction coordinate A measure of the progress of a reaction, plotted on the *x*-axis in an energy diagram.

Reaction intermediate An unstable species that lies in an energy minimum between two transition states.

Reaction mechanism A step-by-step description of how a chemical reaction occurs.

Rearrangement A reaction in which a carbon group or hydrogen atom shifts its connectivity to another atom within the molecule.

Reducing sugar A carbohydrate that reacts with an oxidizing agent to form an aldonic acid.

Reductive amination The formation of an imine from an aldehyde or a ketone, followed by the reduction of the imine to an amine.

Regioselective reaction A reaction in which one direction of bond forming or bond breaking occurs in preference to all other directions.

Relative nucleophilicity The relative rates at which a nucleophile reacts in a reference nucleophilic substitution reaction.

Resolution Separation of a racemic mixture into its enantiomers.

Resonance The absorption of electromagnetic radiation by a spinning nucleus and the resulting "flip" of its spin from a lower energy state to a higher energy state.

Resonance contributing structures Representations of a molecule or ion that differ only in the distribution of valence electrons.

Resonance energy The difference in energy between a resonance hybrid and the most stable of its hypothetical contributing structures.

Resonance hybrid A molecule or ion that is best described as a composite of a number of contributing structures.

Resonance signal A recording of nuclear magnetic resonance in an NMR spectrum.

Restriction endonuclease An enzyme that catalyzes the hydrolysis of a particular phosphodiester bond within a DNA strand.

Ribosomal RNA (rRNA) A ribonucleic acid found in ribosomes, the sites of protein synthesis.

***R,S* system** A set of rules for specifying the configuration about a stereocenter.

S From the Latin *sinister*, meaning left; used in the *R,S* system to show that the order of priority of groups on a stereocenter is counterclockwise.

Sanger dideoxy method A method, developed by Frederick Sanger, for sequencing DNA molecules.

Saponification Hydrolysis of an ester in aqueous NaOH or KOH to an alcohol and the sodium or potassium salts of a carboxylic acid.

Saturated hydrocarbon A hydrocarbon containing only carbon–carbon single bonds.

Secondary (2°) structure of proteins The ordered arrangements (conformations) of amino acids in localized regions of a polypeptide or protein.

Secondary structure of nucleic acids The ordered arrangement of strands of nucleic acid.

Shells A region of space around a nucleus where electrons are found.

Shielding In NMR spectroscopy, electrons around a nucleus create their own local magnetic fields and thereby shield the nucleus from the applied magnetic field.

Sigma (σ) bond A covalent bond in which the overlap of atomic orbitals is concentrated along the bond axis.

Signal splitting Splitting of an NMR signal into a set of peaks by the influence of neighboring nuclei.

Singlet A signal that consists of one peak; the hydrogens that give rise to the signal have no neighboring nonequivalent hydrogens.

Soap A sodium or potassium salt of a fatty acid.

Solvolysis A nucleophilic substitution reaction in which the solvent is the nucleophile.

Specific rotation Observed rotation of the plane of polarized light when a sample is placed in a tube 1.0 dm long at a concentration of 1.0 g/mL.

Spectroscopy The study of the interaction of matter and electromagnetic radiation.

***sp* Hybrid orbital** An orbital produced by the combination of one *s* atomic orbital and one *p* atomic orbital.

***sp*^{2} Hybrid orbital** An orbital produced by the combination of one *s* atomic orbital and two *p* atomic orbitals.

***sp*^{3} Hybrid orbital** An orbital produced by the combination of one *s* atomic orbital and three *p* atomic orbitals.

Staggered conformation A conformation about a carbon–carbon single bond in which the atoms on one carbon are as far apart as possible from the atoms on the adjacent carbon.

Step-growth polymerization A polymerization in which chain growth occurs in a stepwise manner between difunctional monomers, for example, between adipic acid and hexamethylenediamine to form Nylon 66. Also referred to as condensation polymerization.

Stereocenter An atom at which the interchange of two atoms or groups of atoms bonded to it produces a different stereoisomer.

Stereoisomers Isomers that have the same molecular formula and the same connectivity, but different orientations of their atoms in space.

Stereoselective reaction A reaction in which one stereoisomer is formed or destroyed in preference to all others that might be formed or destroyed.

Steric factors The ability of groups, because of their size, to hinder access to a reaction site within a molecule.

Steric strain The strain that arises when atoms separated by four or more bonds are forced abnormally close to one another.

Steroid A plant or animal lipid having the characteristic tetracyclic ring structure of the steroid nucleus, namely, three six-membered rings and one five-membered ring.

Strong acid An acid that is completely ionized in aqueous solution.

Strong base A base that is completely ionized in aqueous solution.

Superposable Able to be overlapped onto another object such that all features match exactly.

Tautomers Constitutional isomers that differ in the location of hydrogen and a double bond relative to O, N, or S.

***N*-Terminal amino acid** The amino acid at the end of a polypeptide chain having the free —NH^+_3 group.

Tertiary (3°) structure of proteins The three-dimensional arrangement in space of all atoms in a single polypeptide chain.

Tertiary structure of nucleic acids The three-dimensional arrangement of all atoms of a nucleic acid, commonly referred to as supercoiling.

Thermoplastic A polymer that can be melted and molded into a shape that is retained when it is cooled.

Thermosetting plastic A polymer that can be molded when it is first prepared, but, once cooled, hardens irreversibly and cannot be remelted.

Thioester An ester in which the oxygen atom of the —OR group is replaced by an atom of sulfur.

Thiohemiacetal A compound analogous to a hemiacetal in which one or more oxygen atoms are replaced by sulfur.

Thiol A compound containing an —SH (sulfhydryl) group.

Torsional strain (also called eclipsed interaction strain) Strain that arises when atoms separated by three bonds are forced from a staggered conformation to an eclipsed conformation.

Trans A prefix meaning "across from."

Transfer RNA (tRNA) A ribonucleic acid that carries a specific amino acid to the site of protein synthesis on ribosomes.

Transition state An unstable species of maximum energy formed during the course of a reaction; a maximum on an energy diagram.

Triglyceride (triacylglycerol) An ester of glycerol with three fatty acids.

Tripeptide A molecule containing three amino acid units, each joined to the next by a peptide bond.

Triplet A signal that is split into three peaks; the hydrogens that give rise to the signal have two neighboring nonequivalent hydrogens that are equivalent to each other.

Unimolecular reaction A reaction in which only one species is involved in the reaction leading to the transition state of the rate-determining step.

Unsaturated hydrocarbon A hydrocarbon containing at least one carbon–carbon pi bond.

Upfield A term used to refer to the relative position of a signal on an NMR spectrum. Upfield indicates a peak to the right of the spectrum (a stronger applied field).

Valence electrons Electrons in the valence (outermost) shell of an atom.

Valence shell The outermost electron shell of an atom.

Vibrational infrared The portion of the infrared region that extends from 4000 to 400 cm^{-1}.

Wavelength (λ) The distance between two consecutive identical points on a wave.

Wavenumber ($\bar{\nu}$) A characteristic of electromagnetic radiation equal to the number of waves per centimeter.

Weak acid An acid that only partially ionizes in aqueous solution.

Weak base A base that only partially ionizes in aqueous solution.

Z From the German *zusammen*, meaning together; specifies that groups of higher priority on the carbons of a double bond are on the same side.

Zaitsev's rule A rule stating that the major product from a *β*-elimination reaction is the most stable alkene; that is, the major product is the alkene with the greatest number of substituents on the carbon–carbon double bond.

Zwitterion An internal salt of an amino acid.

CHAPTER 1 Covalent Bonding and Shapes of Molecules

Problems

1.1 The two elements in each pair have the same number of electrons in the outermost shell of orbitals (valence shell).

(a) Carbon = $1s^2 2s^2 2p^2$ Silicon = $1s^2 2s^2 2p^6 3s^2 3p^2$

(b) Oxygen = $1s^2 2s^2 2p^4$ Sulfur = $1s^2 2s^2 2p^6 3s^2 3p^4$

(c) Nitrogen = $1s^2 2s^2 2p^3$ Phosphorus = $1s^2 2s^2 2p^6 3s^2 3p^3$

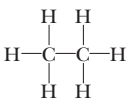
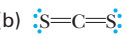
1.2 The electron configuration of the sulfur atom is $1s^2 2s^2 2p^6 \mathbf{3}s^2 \mathbf{3}p^4$. When sulfur gains two electrons to form S^{2-}, the electron configuration becomes $1s^2 2s^2 2p^6 \mathbf{3}s^2 \mathbf{3}p^6$. The valence shell has a full octet and corresponds to the configuration of the noble gas Ar.

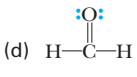
1.3 (a) Li (b) N (c) C (d) O (e) O

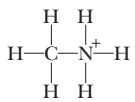
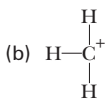
1.4

Bond	Type of bond
S—H	nonpolar covalent
P—H	nonpolar covalent
C—F	polar covalent
C—Cl	polar covalent

1.5 (a) $\overset{\delta+}{C}—\overset{\delta-}{N}$ (b) $\overset{\delta+}{N}—\overset{\delta-}{O}$ (c) $\overset{\delta+}{C}—\overset{\delta-}{Cl}$

1.6 (a)  (b) 

(c) (d) 

1.7 (a)  (b) 

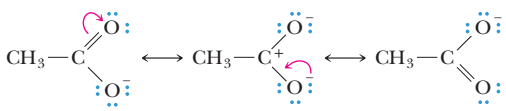
1.8 CH_3OH: all 109.5°

CH_2Cl_2: all 109.5°

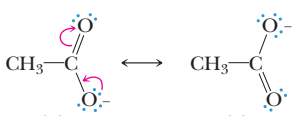
H_2CO_3: 109.5° and 120°

1.9 The linear shape of CO_2 results in a cancellation of the dipole moments. In SO_2, which has a bent shape, the dipole moments do not cancel out.

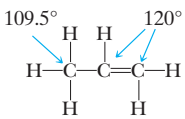
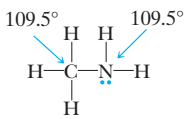
1.10 Pairs (a) and (c).

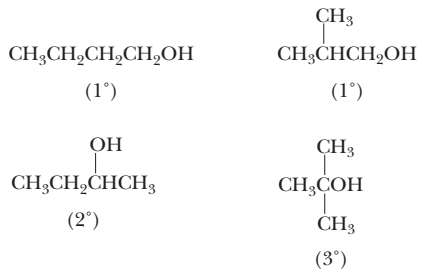
1.11 

(a) (b) (c)

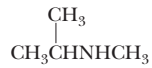


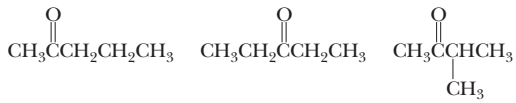
(a) (c)

1.12 (a)  (b) 

1.13 

(1°) (1°) (2°) (3°)

1.14 $CH_3CH_2NHCH_2CH_3$ $CH_3CH_2CH_2NHCH_3$ 

1.15 

1.16 $CH_3CH_2CH_2COOH$ $(CH_3)_2CHCOOH$

$CH_3CH_2COOCH_3$ $CH_3COOCH_2CH_3$

$HCOOCH_2CH_2CH_3$ $HCOOCH(CH_3)_2$

End-of-Chapter Problems

Electronic Structure of Atoms

1.17 (a) Sodium = $1s^2 2s^2 2p^6 3s^1$

(b) Magnesium = $1s^2 2s^2 2p^6 3s^2$

(c) Oxygen = $1s^2 2s^2 2p^4$

(d) Nitrogen = $1s^2 2s^2 2p^3$

(e) Potassium = $1s^2 2s^2 2p^6 3s^2 3p^6 4s^1$

(f) Aluminum = $1s^2 2s^2 2p^6 3s^2 3p^1$

(g) Phosphorus = $1s^2 2s^2 2p^6 3s^2 3p^3$

(h) Argon = $1s^2 2s^2 2p^6 3s^2 3p^6$

1.19 (a) S (b) O (c) C (d) Cl

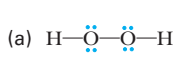
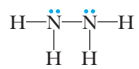
1.21 The *valence shell* of an atom is the outermost shell that can be occupied by electrons in the ground state. The valence shell generally has the highest principal quantum number (n). A *valence electron* is an electron that is situated in the valence shell. Valence electrons are more important because they are the electrons involved in bond formation.

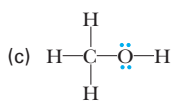
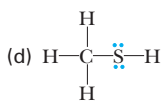
1.23 (a) 0 (b) 2 (c) 8 (d) 6 (e) 8

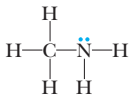
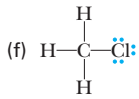
Lewis Structures

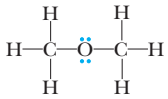
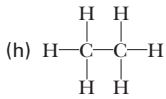
1.25

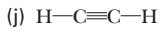
(a) Li—F	ionic
(b) C—F	polar covalent
C—H	nonpolar covalent
(c) Mg—Cl	polar covalent
(d) H—Cl	polar covalent

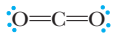
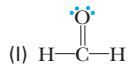
1.27 (a)  (b) 

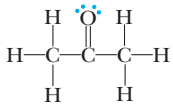
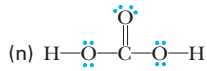
(c)  (d) 

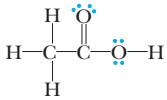
(e)  (f) 

(g)  (h) 

(i)  (j) 

(k)  (l) 

(m)  (n) 

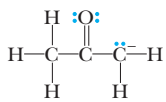
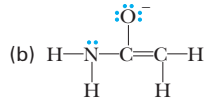
(o) 

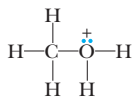
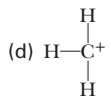
1.29 (a) If carbon were bonded to five hydrogen atoms, the octet rule would be violated. Furthermore, each hydrogen atom can only bond with one other atom, so there is no stable connectivity of the formula CH_5.

(b) Each hydrogen atom can only bond with one other atom, so a single hydrogen atom cannot be bonded to both carbons.

(c) The proton, H^+, does not contain any electrons, so it is not possible to form a bond between two protons.

(d) Nitrogen would exceed its octet.

1.31 (a)  (b) 

(c)  (d) 

1.33 Given the electronegativity difference between Ag and O, the bonding is polar covalent in Ag_2O.

1.35 a

1.37 (a) C—H < N—H < O—H

(b) C—I < C—H < C—Cl

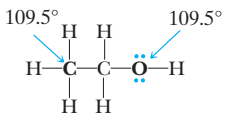
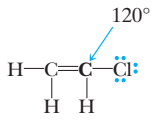
(c) C—C < C—N < C—O

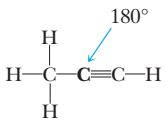
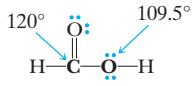
(d) C—Hg < C—Mg < C—Li

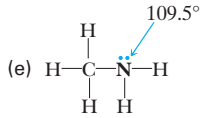
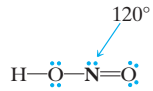
1.39 (a) O—H (b) C—F (c) O—H

(d) O—H (e) O—H (f) C═O

Bond Angles and Shapes of Molecules

1.41 (a)  (b) 

(c)  (d) 

(e)  (f) 

1.43 109.5°

Polar and Nonpolar Molecules

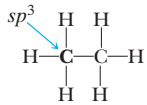
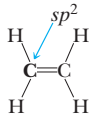
1.45 

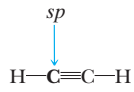
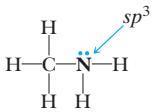
Contributing Structures

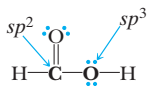
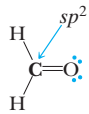
1.47 a, b, d, e, f, and g

1.49 The bond angle of the carbon atom involved in resonance remains at 120° and does not change from one contributing structure to another. The carbon atom in the CH_3 group of pair (c) has a bond angle of 109.5°.

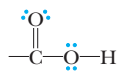
Hybridization of Atomic Orbitals

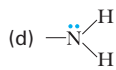
1.51 (a)  (b) 

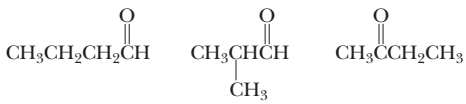
(c)  (d) 

(e)  (f) 

Functional Groups

1.53 (a)  (b) 

(c)  (d) 

1.55 (a) 

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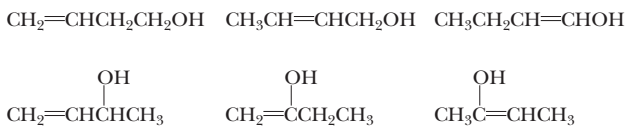
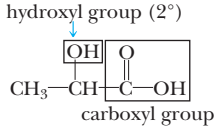
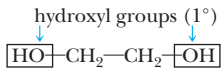
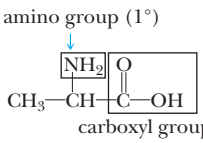
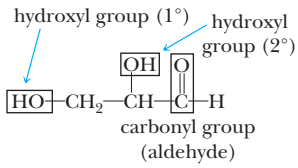
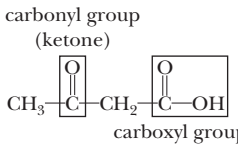


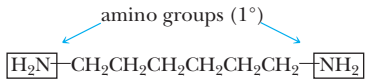
1.57 (a) 

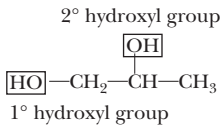
(b) 

(c) 

(d) 

(e) 

(f) 

1.59 

1.61 CO_2 is linear, while O_3 is bent. All atoms in both molecules are sp^2-hybridized.

Looking Ahead

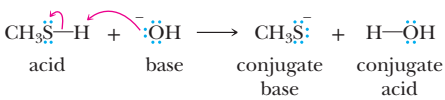
1.63 The two terminal carbon atoms are sp^2-hybridized. Although the carbon chain is linear and the two terminal carbon atoms are trigonal planar, the molecule is not flat.

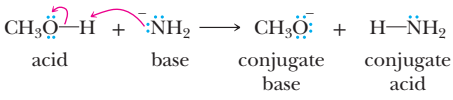
1.65 (a) 6 (b) 120° (c) sp^2

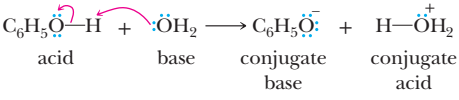
1.67 (a) 120° (b) sp^2 (c) planar

CHAPTER 2 Acids and Bases

Problems

2.1 (a) 

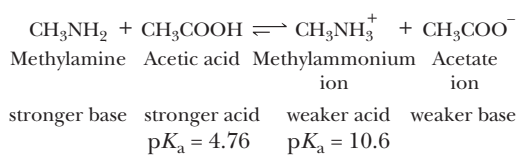
(b) 

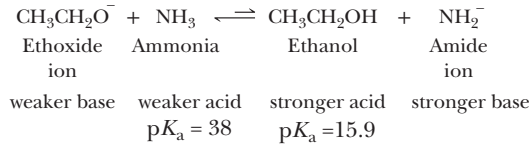
(c) 

2.2 (a) Acetic acid $pK_a = 4.76$

(b) Water $pK_a = 15.7$

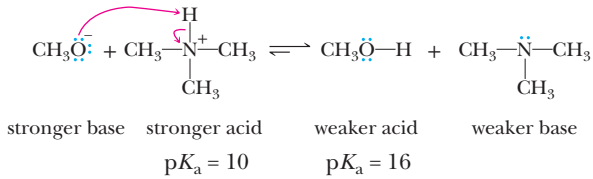
Acetic acid is a stronger acid.

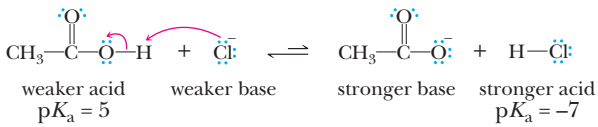
2.3 (a) 

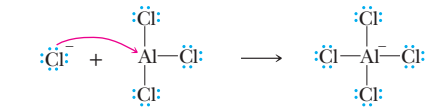
(b) 

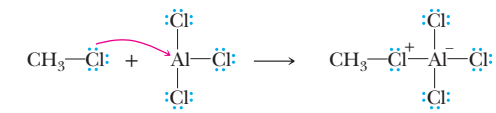
2.4 (a) 2 > 1 > 3

(b) 3 > 1 > 2

2.5 (a) 

(b) 

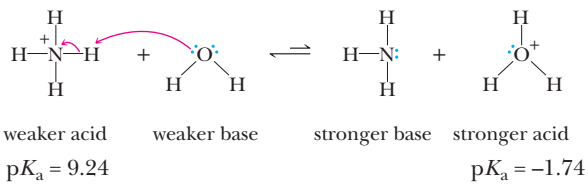
2.6 (a) 

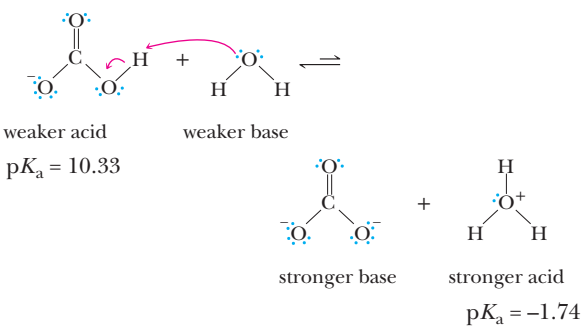
(b) 

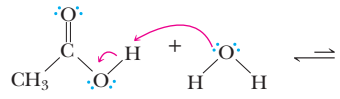
End-of-Chapter Problems

Anhenius Acids and Bases

2.7

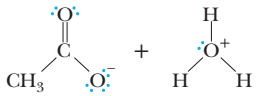
(a) 

(b) 

(c) 

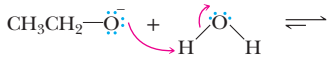
weaker acid weaker base

$pK_a = 4.76$



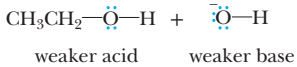
stronger base stronger acid

$pK_a = -1.74$

(d) 

stronger base stronger acid

$pK_a = 15.7$



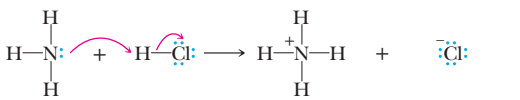
weaker acid weaker base

$pK_a = 15.9$

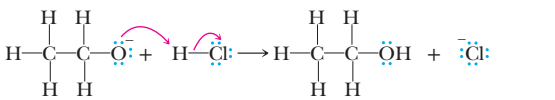
Brønsted–Lowry Acids and Bases

2.9 According to Brønsted–Lowry theory, acids are proton (H^+) donors. The formulas of a conjugate acid–base pair therefore differ by one hydrogen atom, as well as one charge. The acid has one hydrogen atom more, but one negative charge less, than the base.

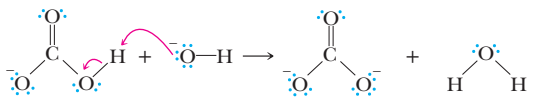
2.11

(a) 

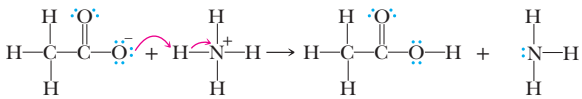
base acid conjugate acid conjugate base

(b) 

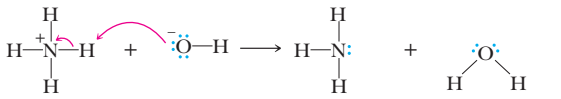
base acid conjugate acid conjugate base

(c) 

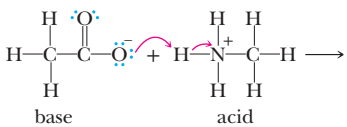
acid base conjugate base conjugate acid

(d) 

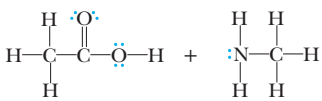
base acid conjugate acid conjugate base

(e) 

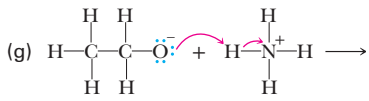
acid base conjugate base conjugate acid

(f) 

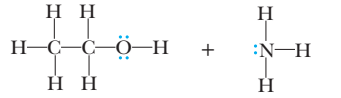
base acid



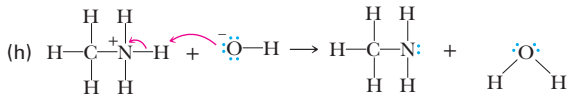
conjugate acid conjugate base

(g) 

base acid

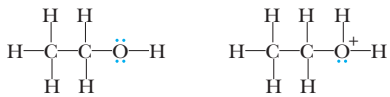


conjugate acid conjugate base

(h) 

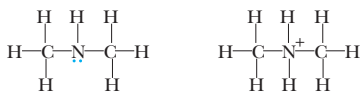
acid base conjugate base conjugate acid

Bases **Conjugate acids**

2.13 (a) 

(b) 

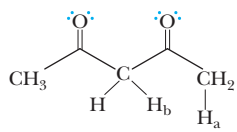
(c) $HC{\equiv}C^-$ $HC{\equiv}C{-}H$

(d) 

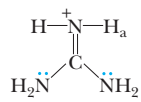
(e) 

(f) 

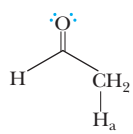
2.15 (a) H_b is the most acidic proton.



(b) H_a is the most acidic proton.

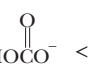


(c) H_a is the most acidic proton.



Quantitative Measure of Acid Strength

2.17 (a) Pyruvic acid (b) Phosphoric acid
(c) Acetylsalicylic acid (d) Acetic acid

2.19 (a)  < NH_3 < $CH_3CH_2O^-$

(b) $CH_3\overset{O}{\overset{\|}{C}}O^- < HO\overset{O}{\overset{\|}{C}}O^- < HO^-$

(c) $H_2O < CH_3\overset{O}{\overset{\|}{C}}O^- < NH_3$

(d) $CH_3\overset{O}{\overset{\|}{C}}O^- < OH^- < NH_2^-$

2.21 H_2S ionizes to form a conjugate base (HS^-) that is more stable than the conjugate base of H_2O (HO^-).

Position of Equilibrium in Acid–Base Reactions

2.23 $HO\overset{O}{\overset{\|}{C}}OH \longrightarrow CO_2 + H_2O$

2.25 (a) $CH_3COOH + HCO_3^- \rightleftharpoons CH_3COO^- + H_2CO_3$
$pK_a = 4.76$ $pK_a = 6.36$

(b) $CH_3COOH + NH_3 \rightleftharpoons CH_3COO^- + NH_4^+$
$pK_a = 4.76$ $pK_a = 9.24$

(c) $CH_3COOH + H_2O \rightleftharpoons CH_3COO^- + H_3O^+$
$pK_a = 4.76$ $pK_a = -1.74$

(d) $CH_3COOH + OH^- \rightleftharpoons CH_3COO^- + H_2O$
$pK_a = 4.76$ $pK_a = 15.7$

2.27 In acid–base equilibria, the position of the equilibrium favors the reaction of the stronger acid and stronger base to give the weaker acid and weaker base.

Relationship Between Acidity and Basicity and Molecular Structure

2.29 (a) The oxygen of the carbonyl group is more basic because it has a partial negative charge.

(b) For the same reason as (a), the N is more basic. However, in this case, there is an additional effect: Because N is lower in electronegativity than O, the N is even more likely to accept a proton.

(c) The carbon on the left is more basic because the carbon on the right is stabilized by resonance. Furthermore, the delocalization of the negative charge of the carbon on the right increases the negative charge of the carbon on the left.

(d) The amine is more basic than the alcohol because nitrogen has a lower electronegativity than does oxygen.

Lewis Acids and Bases

2.31

(a) $CH_3{-}\overset{+}{C}H{-}CH_3 + CH_3{-}\ddot{O}{-}H \longrightarrow CH_3{-}\overset{H}{\overset{|}{\overset{+}{O}}}{-}CH_3$ (H, CH_3, H)
Lewis acid Lewis base

(b) $CH_3{-}\overset{+}{C}H{-}CH_3 + :\ddot{B}r:^- \longrightarrow CH_3{-}\overset{:Br:}{\overset{|}{C}}{-}CH_3$ (H)
Lewis acid Lewis base

(c) $CH_3{-}\overset{CH_3}{\overset{|}{\overset{+}{C}}}{-}CH_3 + H{-}\ddot{O}{-}H \longrightarrow CH_3{-}\overset{CH_3}{\overset{|}{\overset{+}{O}}}{-}H$ (CH_3, H)
Lewis acid Lewis base

Looking Ahead

2.33 (a) $CH_3CH_2OH + HCO_3^- \rightleftharpoons CH_3CH_2O^- + H_2CO_3$
$pK_a = 15.9$ $pK_a = 6.36$

(b) $CH_3CH_2OH + OH^- \rightleftharpoons CH_3CH_2O^- + H_2O$
$pK_a = 15.9$ $pK_a = 15.7$

(c) $CH_3CH_2OH + NH_2^- \rightleftharpoons CH_3CH_2O^- + NH_3$
$pK_a = 15.9$ $pK_a = 38$

(d) $CH_3CH_2OH + NH_3 \rightleftharpoons CH_3CH_2O^- + NH_4^+$
$pK_a = 15.9$ $pK_a = 9.24$

2.35 Benzoic acid will dissolve in all four solutions.

2.37 The conjugate base of dimethyl ether is a highly unstable C^- ion that is stabilized by only the inductive effect of the electronegative oxygen atom. As a result, dimethyl ether is not very acidic.

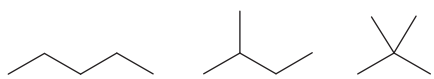
2.39 Amino acids are bifunctional in that they contain both basic (amino) and acidic (carboxyl) groups. These groups undergo an intramolecular acid–base reaction to give structural formula (B), which is the better representation of alanine.

CHAPTER 3 Alkanes and Cycloalkanes

Problems

3.1 (a) Constitutional isomers (b) Same compound

3.2



3.3 (a) 5-Isopropyl-2-methyloctane
(b) 4-Isopropyl-4-propyloctane
(c) 4-Ethyl-2,3-dimethylheptane
(d) 4,6-Diisopropyl-2-methylnonane

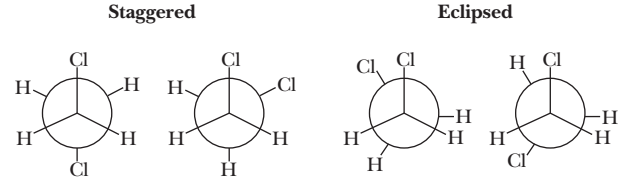
3.4 (a) $CH_3\overset{1^\circ}{\overset{|}{C}}H{-}CH_2{-}CH_2{-}CH_3$ (1° 3° 2° 2° 1°)

(b) $CH_3{-}CH_2{-}\overset{CH_3\ CH_3}{\overset{|\quad|}{C}}{-}\overset{3^\circ}{CH}$ (1° 2° 1° 1° 1° 1°)

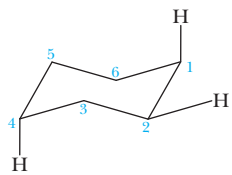
3.5 (a) C_9H_{18} Isobutylcyclopentane
(b) $C_{11}H_{22}$ *sec*-Butylcycloheptane
(c) C_6H_{12} 1-Ethyl-1-methylcyclopropane
(d) $C_{10}H_2O$ *tert*-Butylcyclohexane

3.6 (a) Propanone (b) Pentanal
(c) Cyclopentanone (d) Cycloheptene

3.7

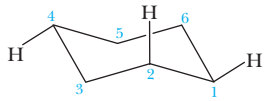


3.8 (a)



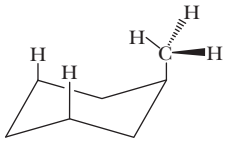
(b) The hydrogen on carbon 2 is equatorial, and the hydrogens on carbons 1 and 4 are axial.

(c)

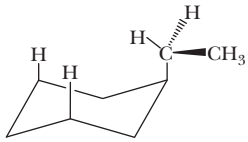


The hydrogen atom on carbon 1 is now equatorial, the hydrogen atom on carbon 2 is now axial, and the hydrogen atom on carbon 4 is now equatorial.

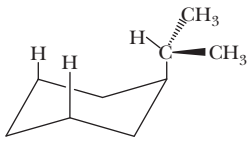
3.9 An axial *tert*-butyl group will always have a $—CH_3$ group directed at the other axial substituents, while the methyl, ethyl, and isopropyl groups of the other three compounds can adopt a conformation where the $—CH_3$ groups face away from the other axial positions.



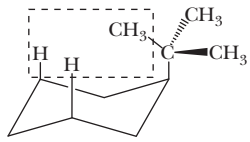
methyl substituent



ethyl substituent

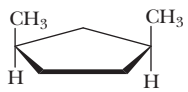


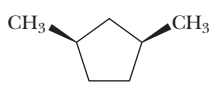
isopropyl substituent



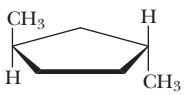
tert-butyl substituent

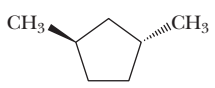
3.10 (a)





cis-1,3-Dimethylcyclopentane

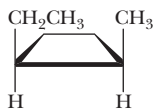


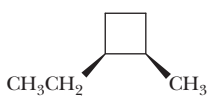


trans-1,3-Dimethylcyclopentane

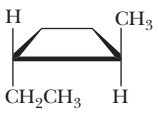
(b) *cis–trans* isomerism is not possible.

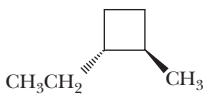
(c)





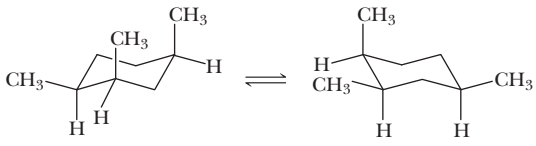
cis-1-Ethyl-2-methylcyclobutane





trans-1-Ethyl-2-methylcyclobutane

3.11



less stable more stable

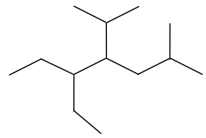
3.12 (a) 2,2-Dimethylpropane < 2-Methylbutane < Pentane

(b) 2,2,4-Trimethylhexane < 3,3-Dimethylheptane < Nonane

End-of-Chapter Problems

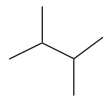
Structure of Alkanes

3.13 (a)

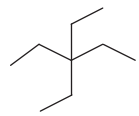


(b)

(c)

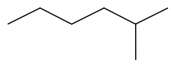


(d)



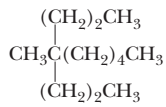
(e)

(f)



3.15 (a) $CH_3(CH_2)_4CH(CH_3)_2$ (b) $HC(CH_2CH_2CH_3)_3$

(c)



(d) $(CH_3)_2C(CH_2)_3CH(CH_3)_2$

Constitutional Isomerism

3.17 (1) Compounds (a) and (g) represent the same compound. Compounds (d) and (e) represent the same compound.

(2) Compounds (a = g), (d = e), and (f) represent constitutional isomers of $C_4H_{10}O$.

Compounds (b) and (c) represent constitutional isomers C_4H_8O.

(3) The isomers of $C_4H_{10}O$ [(a = g) and (d = e)] are different compounds from the isomers of C_4H_8O [(b) and (c)], and all are different from compound (h).

3.19 (1) None of the compounds are the same.

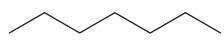
(2) Compounds (a), (d), and (e) represent constitutional isomers of C_4H_8O.

Compounds (c) and (f) represent constitutional isomers of $C_5H_{10}O$.

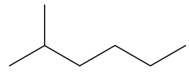
Compounds (g) and (h) represent constitutional isomers of $C_6H_{10}O$.

(3) Compound (b), with formula C_5H_8O, is a different compound than all of the isomers listed for each of the respective molecular formulas indicated in (2).

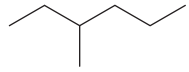
3.21



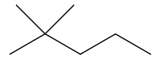
Heptane



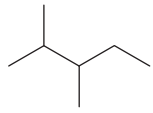
2-Methylhexane



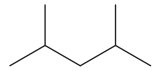
3-Methylhexane



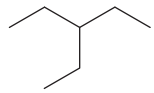
2,2-Dimethylpentane



2,3-Dimethylpentane

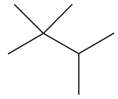


2,4-Dimethylpentane



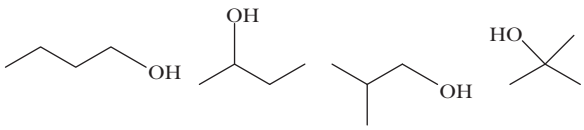
3-Ethylpentane

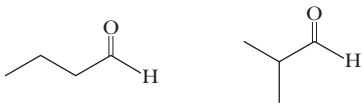
3,3-Dimethylpentane

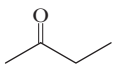


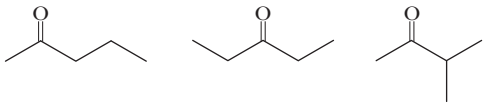
2,2,3-Trimethylbutane

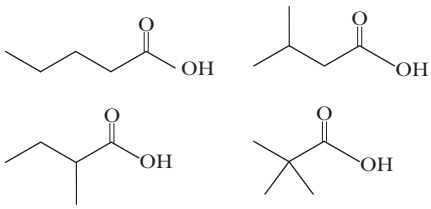
3.23

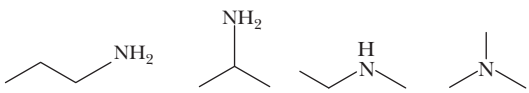
(a) 

(b) 

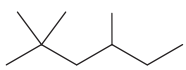
(c) 

(d) 

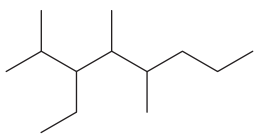
(e) 

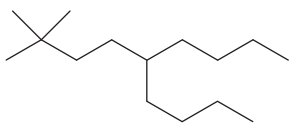
(f) 

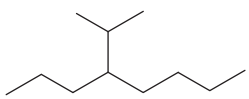
Nomenclature of Alkanes and Cycloalkanes

3.25 (a) 

(b) 

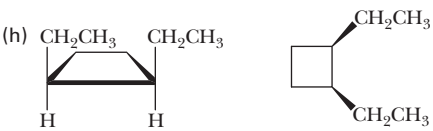
(c) 

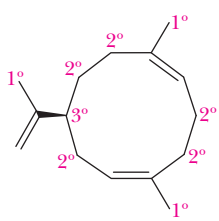
(d) 

(e) 

(f) 

(g) 

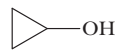
(h) 

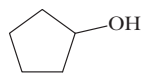
3.27 

3.29 (a) CH_3CH_2OH (b) $CH_3\overset{\overset{O}{\|}}{C}H$

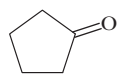
(c) $CH_3\overset{\overset{O}{\|}}{C}OH$ (d) $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_3$

(e) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$ (f) $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH$

(g) $CH_3CH_2\overset{\overset{O}{\|}}{C}H$ (h) 

(i) 

(j) 

(k) 

(l) $CH_3(CH_2)_5\overset{\overset{O}{\|}}{C}OH$

Conformations of Alkanes and Cycloalkanes

3.31 2-Methylpropane has only one staggered conformation and one eclipsed conformation.

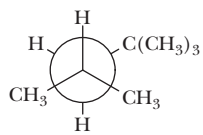
3.33 (a) Although the molecule is in a staggered conformation, the two methyl groups are next to one another, increasing steric strain.

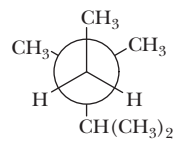
(b) Being an eclipsed conformation, the molecule experiences high torsional strain.

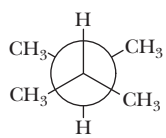
(c) The methyl and *tert*-butyl groups are in close proximity, increasing steric strain.

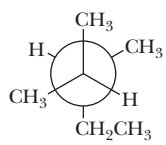
(d) The ethyl and isopropyl groups, which are the two largest groups, are in close proximity.

3.35 (b)

3.37 (a) 

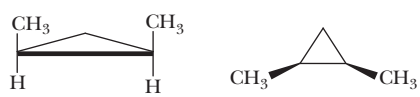
(b) 

(c) 

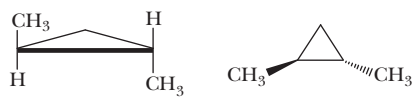
(d) 

cis–trans Isomerism in Cycloalkanes

3.39 The cyclic structure of a cycloalkane prevents full 360° rotation about the C—C bond axis, allowing two possible spatial orientations of the substituents bonded to each sp^3 carbon.

3.41 

cis-1,2-Dimethylcyclopropane



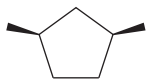
trans-1,2-Dimethylcyclopropane

3.43

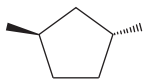
(a) 

cis-1,2-Dimethylcyclopentane *trans*-1,2-Dimethylcyclopentane

(b)



cis-1,3-Dimethylcyclopentane



trans-1,3-Dimethylcyclopentane

3.45

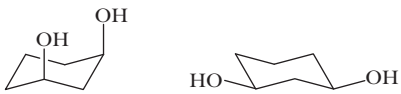
Position of substitution	*cis*	*trans*
1,2-	a,e or e,a	e,e or a,a
1,3-	e,e or a,a	a,e or e,a
1,4-	a,e or e,a	e,e or a,a

3.47

(a)

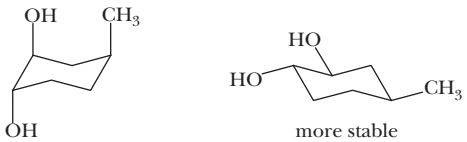
chairs are of equal stability

(b)



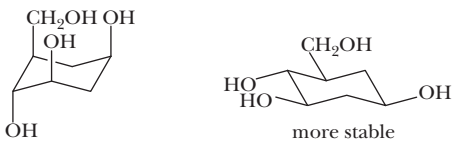
more stable

(c)



more stable

(d)



more stable

Physical Properties of Alkanes and Cycloalkanes

3.49 Highest boiling point: heptane

Lowest boiling point: 2,2-dimethylpentane

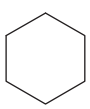
3.51 Heptane has a boiling point of 98 °C. Its molecular formula is C_7H_{16}, which corresponds to a molecular weight of 100 g/mol. Although the molecular weight of water is 5.5 times lower, the relatively strong hydrogen bonding forces hold the molecules of liquid water together. On the contrary, only the relatively weak dispersion forces exist in heptane.

3.53 (a) No (b) Yes (c) Yes (d) Liquid (e) Less

Reactions of Alkanes

3.55 (a) $2CH_3(CH_2)_4CH_3 + 19O_2 \longrightarrow 12CO_2 + 14H_2O$

(b)



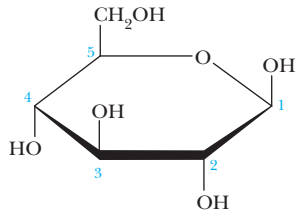
$+ \quad 9O_2 \longrightarrow 6CO_2 + 6H_2O$

(c) $2CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2CH_3 + 19O_2 \longrightarrow 12CO_2 + 14H_2O$

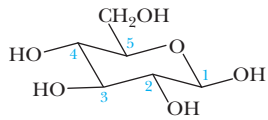
3.57 2,2,4-trimethylpentane on both a per mole and per gram basis

Looking Ahead

3.59 (a)



(b)



All the hydrogens are axial, and all the other substituents are equatorial.

3.61 (a) Rings A, B, and C are in the chair conformation. Ring D, a cyclopentane ring, is in an envelope conformation.

(b) The hydroxyl group on ring A is equatorial.

(c) The methyl group at the A/B junction is axial with respect to both rings.

(d) The methyl group at the junction of rings C/D is axial to ring C.

CHAPTER 4 Alkenes and Alkynes

Problems

4.1 (a) 3,3-Dimethyl-1-pentene

(b) 2,3-Dimethyl-2-butene

(c) 3,3-Dimethyl-1-butyne

(d) 2-ethyl-3-methyl-1-butene

(e) 2,4,4-trimethyl-1-pentene

4.2 (a) *cis*-4-Methyl-2-pentene

(b) *trans*-2,2-Dimethyl-3-hexene

4.3 (a) (*E*)-1-Chloro-2,3-dimethyl-2-pentene

(b) (*Z*)-1-Bromo-1-chloropropene

(c) (*E*)-2,3,4-Trimethyl-3-heptene

(d) (*E*)-3-Cyclopentyl-3-hexene

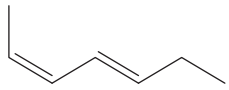
4.4 (a) 1-Isopropyl-4-methylcyclohexene

(b) Cyclooctene

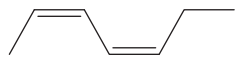
(c) 4-*tert*-Butylcyclohexene

(d) 1-Methylene-3-cyclohexene

4.5



cis,trans-2,4-Heptadiene



cis,cis-2,4-Heptadiene

4.6 4

End-of-Chapter Problems

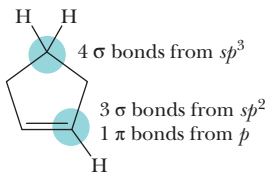
Structure of Alkenes and Alkynes

4.7 (a) The alkene will dissolve in cyclohexane, forming a homogeneous solution.

(b) When nonpolar *trans*-3-heptene is added to ammonia, an immiscible mixture is formed.

4.9 A compound that is *saturated* does not contain any carbon–carbon π bonds. Compounds that are *unsaturated* contain one or more carbon–carbon π bonds.

4.11 (a)



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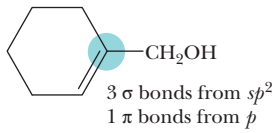

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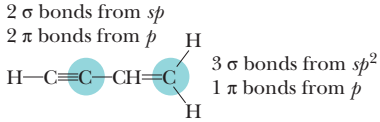

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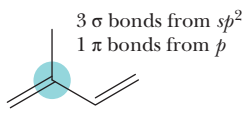
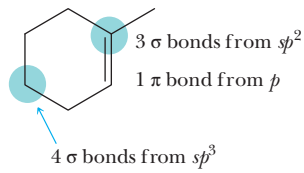


4.13 (a)



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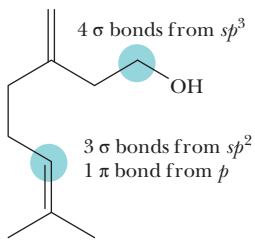

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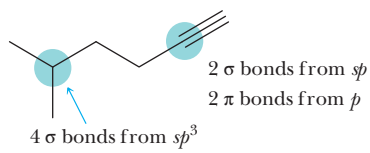

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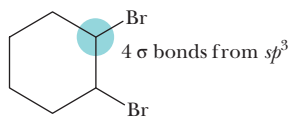
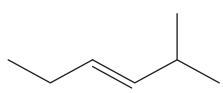


Nomenclature of Alkenes and Alkynes

4.15 (a)



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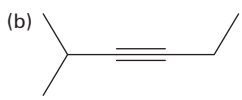

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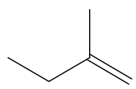

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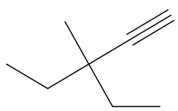

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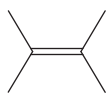

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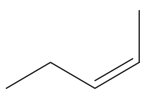

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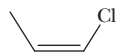

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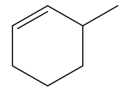


4.17 (a) 1,2-Dimethylcyclohexene

(b) 4,5-Dimethylcyclohexene

(c) 1-*tert*-Butyl-2,4,4-trimethylcyclohexene

(d) (*E*)-1-Cyclopentyl-2-methyl-1-pentene

4.19 (a) The parent chain is four carbons long, and it is also necessary to indicate the configuration (*E* or *Z*). Correct name: 2-butene

(b) The numbering of the chain is incorrect, and it is also necessary to indicate the configuration (*E* or *Z*). Correct name: 2-pentene

(c) The numbering of the ring is incorrect. Correct name: 1-methylcyclohexene

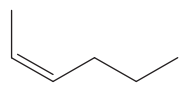
(d) It is necessary to indicate the position of the carbon–carbon double bond. Correct name: 3,3-dimethyl-1-pentene

(e) The numbering of the chain is incorrect. Correct name: 2-hexyne

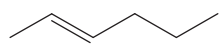
(f) The parent chain is five carbons long, and it is also necessary to indicate the configuration (*E* or *Z*). Correct name: 3,4-dimethyl-2-pentene

Cis–Trans (E/Z) Isomerization in Alkenes and Cycloalkenes

4.21 (b)

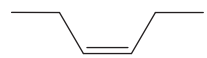


cis-2-Hexene

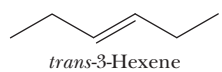


trans-2-Hexene

(c)

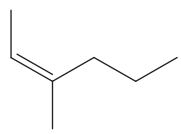


cis-3-Hexene

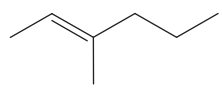


trans-3-Hexene

(e)

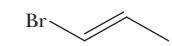


cis-3-Methyl-2-hexene



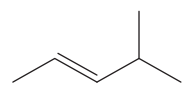
trans-3-Methyl-2-hexene

4.23 (b)



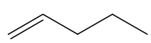
(*E*)-1-Bromopropene

(d)

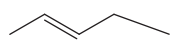


(*E*)-4-Methyl-2-pentene

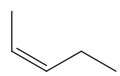
4.25



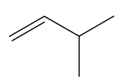
1-Pentene



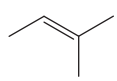
trans-2-Pentene



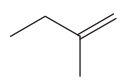
cis-2-Pentene



3-Methyl-1-butene



2-Methyl-2-butene



2-Methyl-1-butene

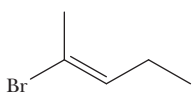
4.27 (a) $-CH_3 < -CH_2CH_3 < -Br$

(b) $-CH(CH_3)_2 < -CH_2CH_2NH_2 < -OCH_3$

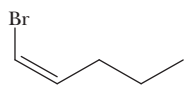
(c) $-CH_2OH < -COOH < -OH$

(d) $-CH(CH_3)_2 < -CH{=}CH_2 < -CH{=}O$

4.29 (a)

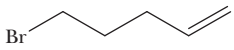


(*E*)-2-Bromo-2-pentene

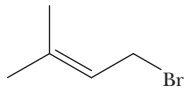


(*Z*)-1-Bromo-1-pentene

(b)

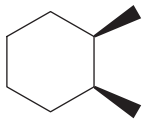


5-Bromo-1-pentene

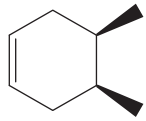


1-Bromo-3-methyl-2-butene

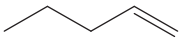
4.31 (b)



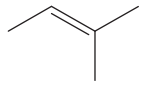
(d)



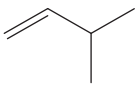
4.33 (a)



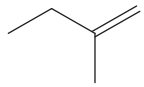
1-Pentene



2-Methyl-2-butene

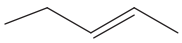


3-Methyl-1-butene

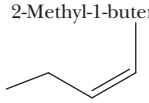


2-Methyl-1-butene

(b)



trans-2-Pentene

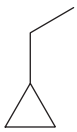


cis-2-Pentene

(c)

Cyclopentane

Methylcyclobutane



Ethylcyclopropane

1,1-Dimethylcyclopropane

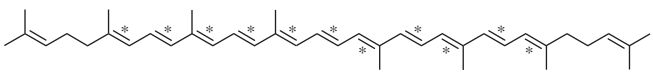
(d)

cis-1,2-Dimethylcyclopropane

trans-1,2-Dimethylcyclopropane

4.35 The *trans* isomer is elaidic acid, and the *cis* isomer is oleic acid.

4.37 *E-Z* isomerism is possible for eleven of the carbon–carbon double bonds, which are indicated (*) in the structure below. All of these double bonds have the *E* configuration.



4.39 (a) *E* (b) 4

Looking Ahead

4.41 The indicated bond in 1,3-butadiene is formed by the overlap of two sp^2-hybridized carbons, while the indicated bond in 1-butene is formed by the overlap of one sp^3-hybridized and one sp^2-hybridized carbon. sp^2-Hybridized orbitals are smaller because they have greater s character (an s orbital holds its electrons closer to the nucleus of an atom), so the bond made from two sp^2 hybrids is shorter.

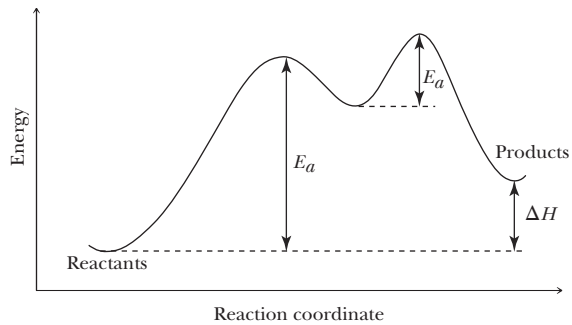
4.43 The electron density surrounding each alkene is affected by the electronegativity of the substituent near it. In molecules (a) and (b), the presence of oxygen and nitrogen, both of which are more electronegative than carbon, the alkenes have a reduced electron density, and the alkene carbon closest to the oxygen or nitrogen atom has a partial positive charge. Whereas the silicon atom in (c) is lower in electronegativity than carbon, the alkene has a higher electron density.

4.45 Fumaric acid has the *E* configuration, and it can be designated as a *trans* alkene. Aconitic acid has the *Z* configuration, and it can be designated as a *trans* alkene (note that while the two COOH groups are *cis* to each other, the C_5 parent chain is *trans*).

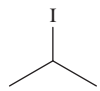
CHAPTER 5 Reactions of Alkenes and Alkynes

Problems

5.1 In an endothermic reaction, the products formed are higher in energy than the reactants. These reactions are thermodynamically unfavorable because they require a net input of heat.

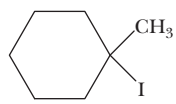


5.2 (a)



2-Iodopropane

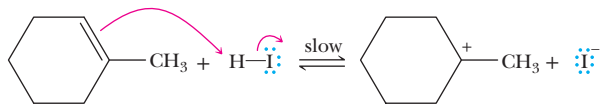
(b)



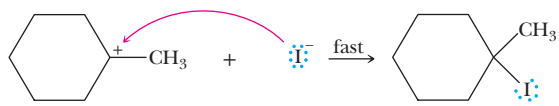
1-Iodo-1-methylcyclohexane

5.3 (a) > (b) > (c)

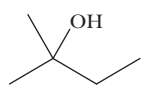
5.4 Step 1: the rate-determining step.



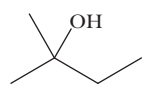
Step 2:



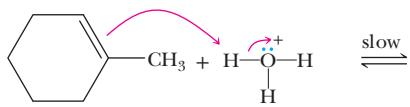
5.5 (a)

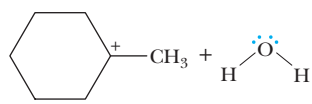


(b)

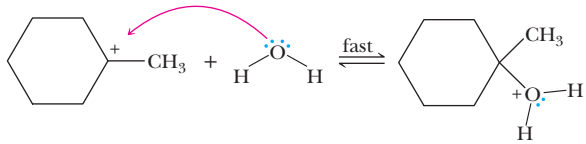


5.6 Step 1: the rate-determining step.

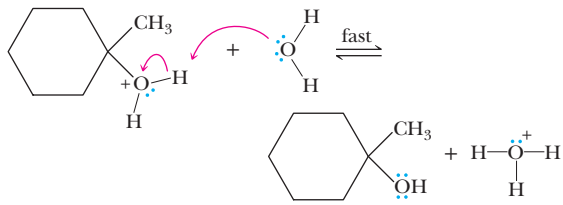




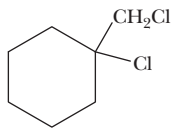
Step 2:



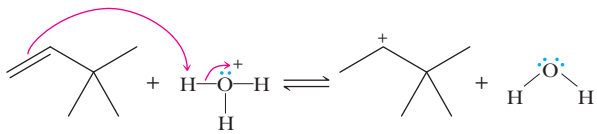
Step 3:



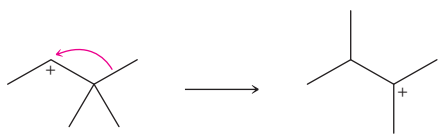
5.7 (a) $CH_3CH(CH_3)CH(Br)CH_2Br$ (b)



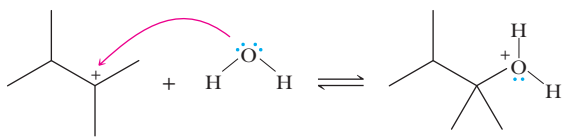
5.8 Step 1:



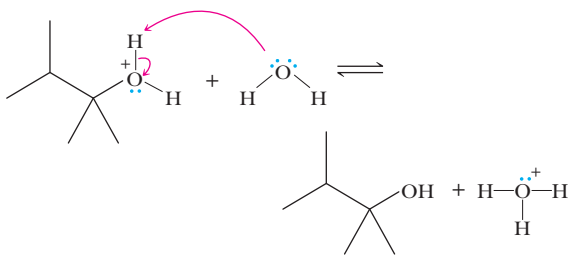
Step 2:



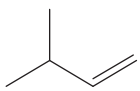
Step 3:



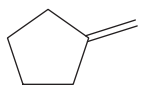
Step 4:



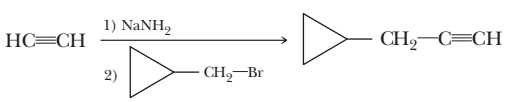
5.9 (a)



(b)



5.10 (a)



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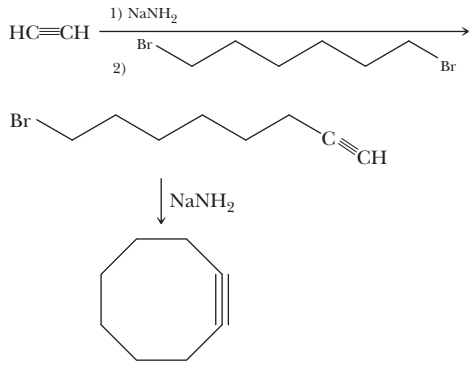
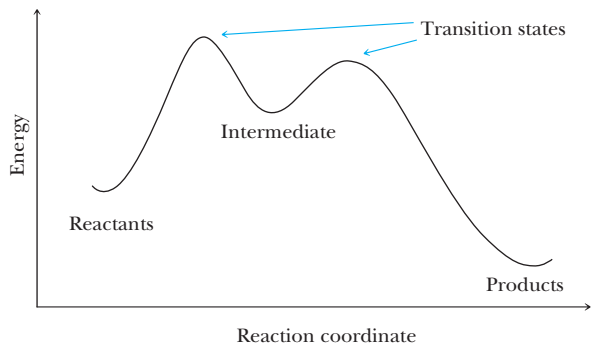


End-of-Chapter Problems

Energy Diagrams

5.11 A transition state is a point on the reaction coordinate where the energy is at a maximum. Because a transition state is at an energy maximum, it cannot be isolated and its structure can often only be postulated. A reaction intermediate corresponds to an energy minimum between two transition states, but the energy of the intermediate is usually higher than the energies of the products or the reactants.

5.13 A two-step reaction has two transition states and one intermediate. The intermediate corresponds to the product of the first step and the reactant for the second step.



Electrophilic Additions to Alkenes, Rearrangements, and Hydroboration–Oxidation

5.15 (a) $CH_3\overset{+}{C}HCH_3$ (b) $CH_3C^{+}(CH_3)CH_2CH_3$

5.17 (a)

3° carbocation (formed more readily) + 2° carbocation

(b)

Both are 2° carbocations and are of equal stability, so they are both formed at approximately equal rates

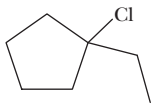
(c)

3° carbocation (formed more readily) + 2° carbocation

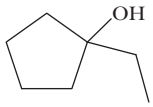
(d)

3° carbocation (formed more readily) + 1° carbocation

5.19 (a)



(b)



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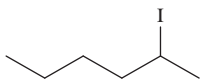

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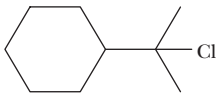

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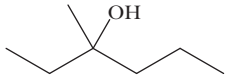

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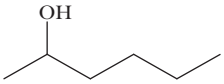
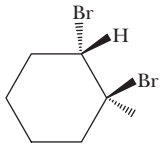


5.21 (a)



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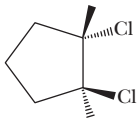
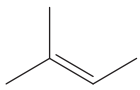


5.23 (a)



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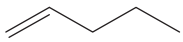

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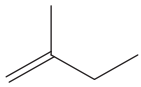

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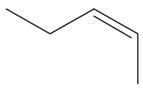

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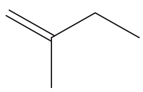

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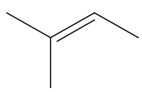
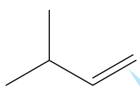
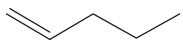


(b)



the carbocation formed from this alkene could rearrange to place the chlorine on the 3° carbon

(c)



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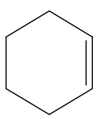

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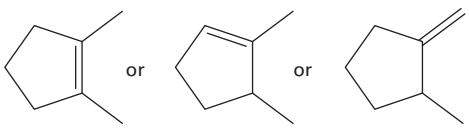

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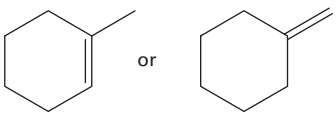

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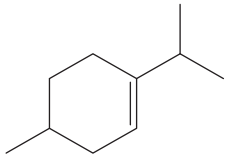

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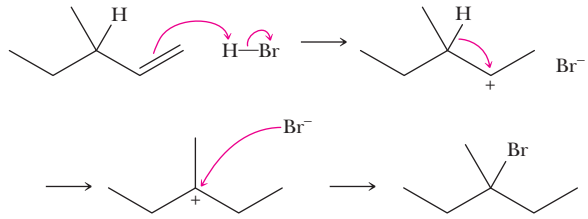

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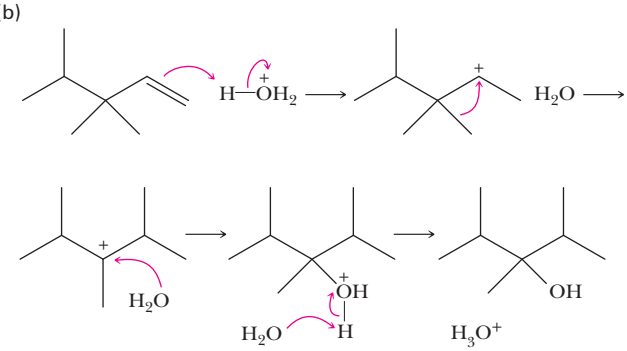

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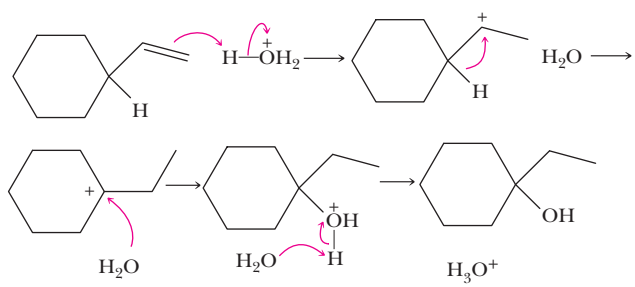

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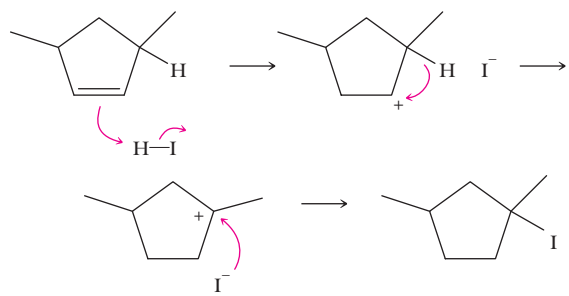

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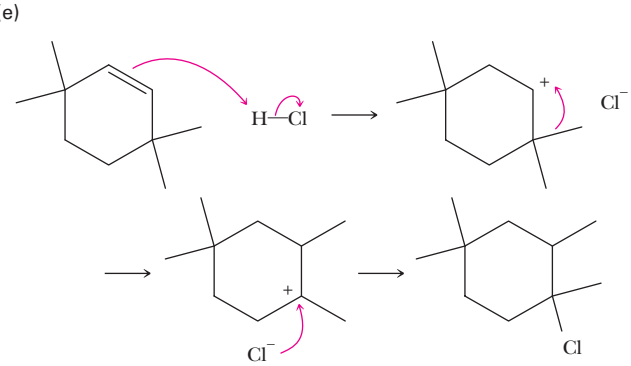

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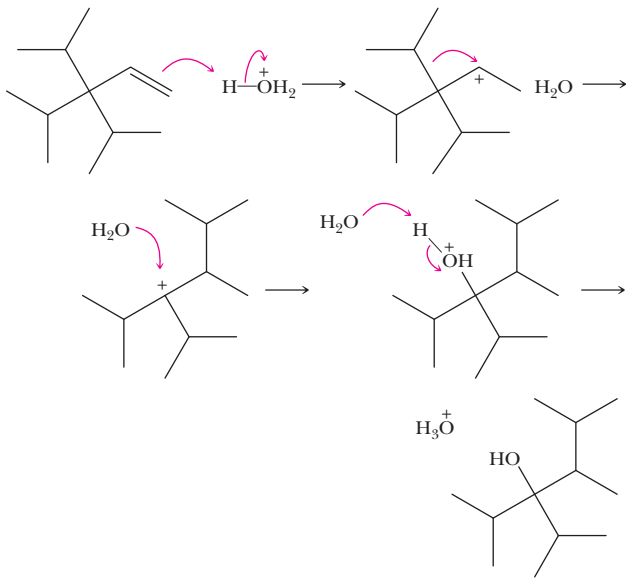
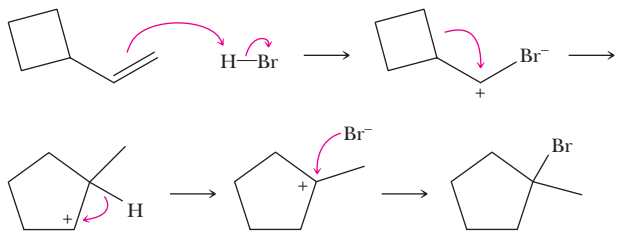


5.31 (a)



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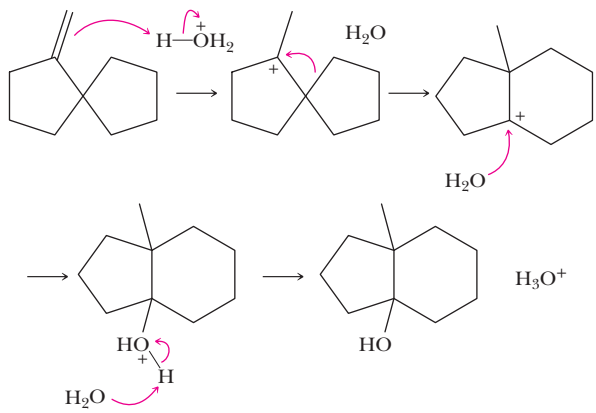

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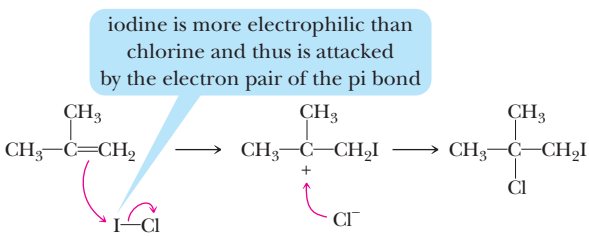
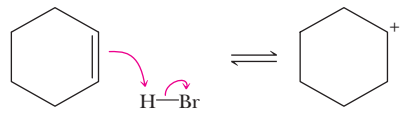
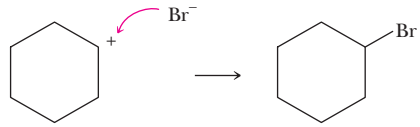


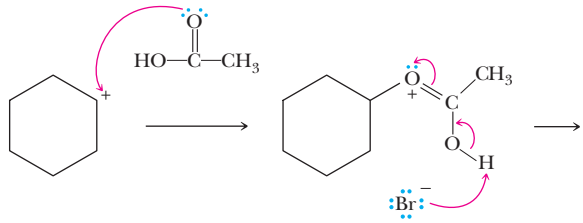
5.35 In the presence of two acids, HBr and acetic acid, the stronger acid (HBr) is more likely to protonate cyclohexene.

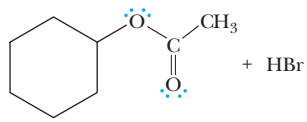


Bromocyclohexane is formed from the nucleophilic attack of the carbocation by Br^-,

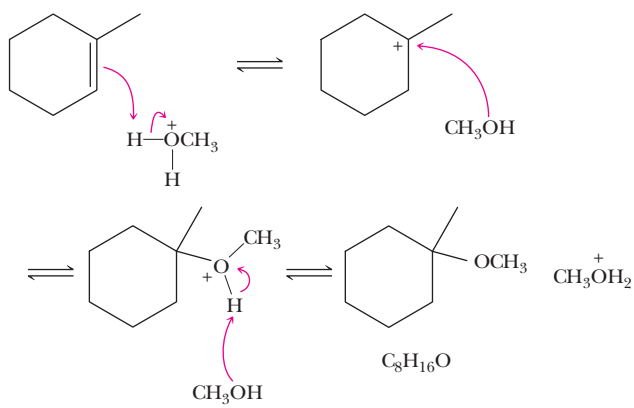


whereas nucleophilic attack by acetic acid followed by deprotonation results in the formation of cyclohexyl acetate.



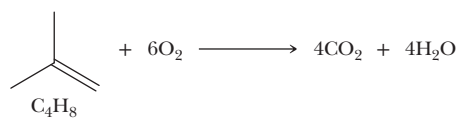


5.37

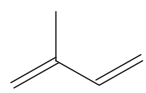


Oxidation–Reduction

5.39

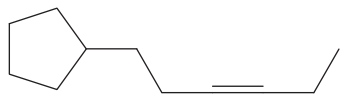


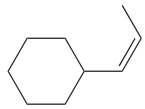
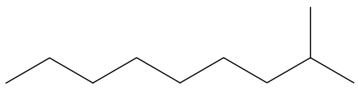
5.41



Reactions of Alkynes

5.43 (a)

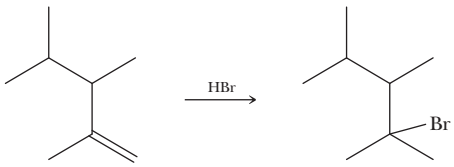


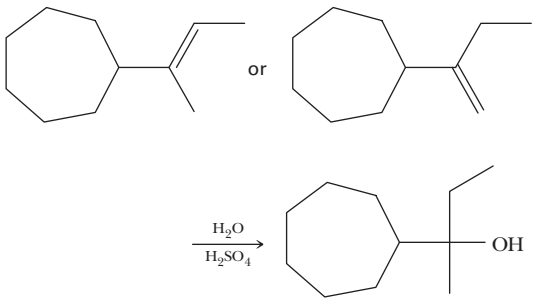
(b)  (c) 

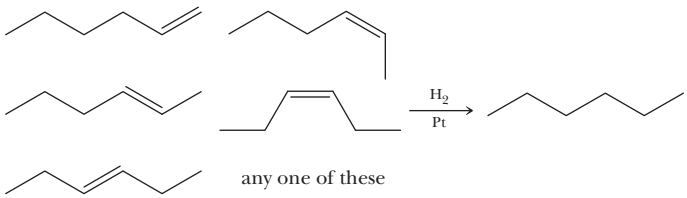
Synthesis

5.45 (a) H_2/Ni (b) H_2O/H_2SO_4 (c) HBr
(d) Br_2 (e) HCl (f) 1) HBr
2) NaC≡CH
3) H_2/Lindlar's

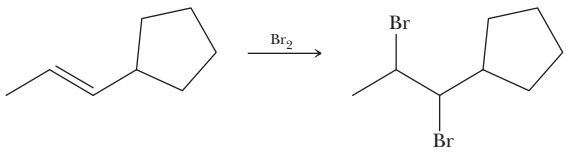
5.47 (a) 1) BH_3 2) H_2O_2, NaOH
(b) H_2O/H_2SO_4
(c) H_2/Ni

5.49 (a) 

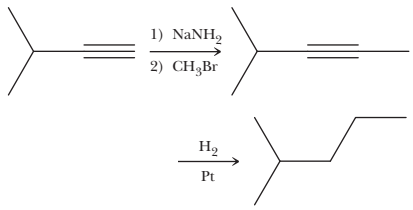
(b) 

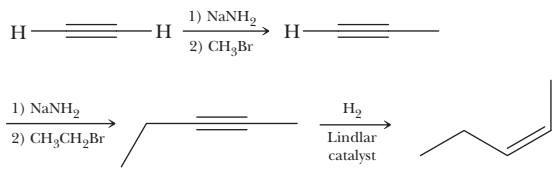
(c) 

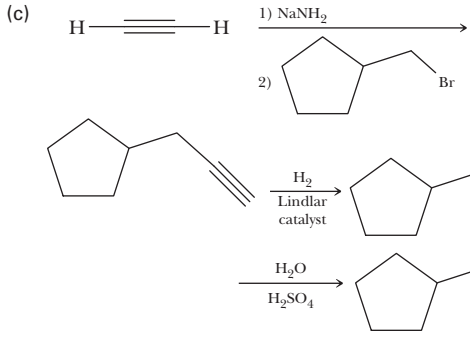
any one of these

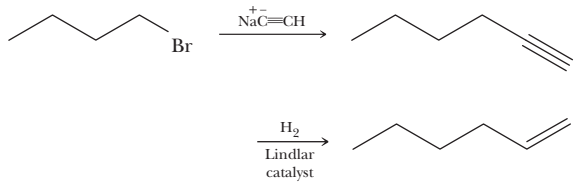
(d) 

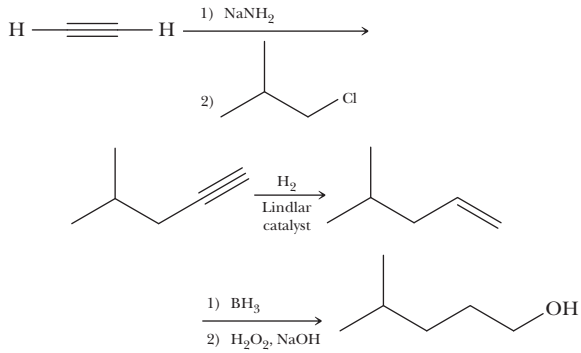
Chemical Transformations

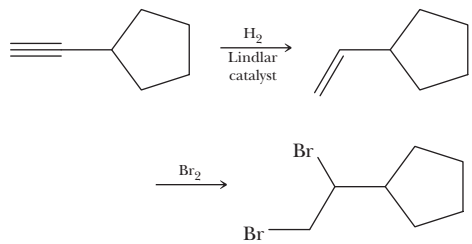
5.51 (a) 

(b) 

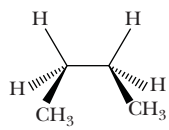
(c) 

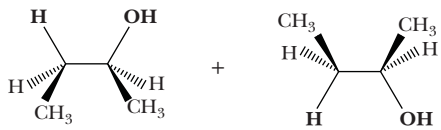
(d) 

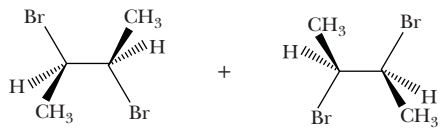
(e) 

(f) 

Looking Ahead

5.53 (a) 

(b) 

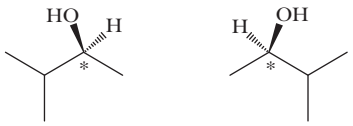
(c) 

CHAPTER 6 Chirality

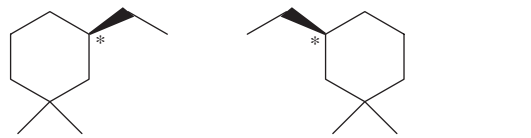
Problems

6.1 (a)

(b)



(c)



(d)

6.2 (a) *S* (b) *S* (c) *R* (d) *S*

6.3 (a) (1) and (3), and (2) and (4)

(b) (1) and (2), (1) and (4), (2) and (3), and (3) and (4)

6.4 (a) (2) and (3) (b) (1) and (4) (c) (2) and (3)

(d) (3) and (4), and (1) and (3)

6.5 3

6.6 2

End-of-Chapter Problems

Chirality

6.7 Stereoisomers are compounds that have the same molecular formula and the same atom connectivity (i.e., they are of the same constitutional isomer) but have different, noninterconverting orientations of their atoms or groups in three-dimensional space.

Four types of stereoisomers include:

- Enantiomers
- Diastereomers
- *cis–trans* isomers
- Meso isomers

6.9 *Conformation* refers to the different, interconverting arrangements of atoms, in three-dimensional space, that are the result of rotation about single bonds. *Configuration* also refers to the different spatial arrangement of atoms, but these spatial arrangements are noninterconverting and cannot be made the same by rotation about single bonds.

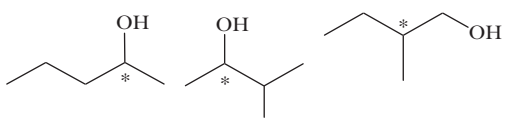
6.11 A spiral with a left-handed twist will have a left-handed twist when viewed from either end.

6.13 This of course depends on the manufacturer of the pasta. However, in any given box of spiral pasta, usually every piece of pasta is of the same twist because the entire box was manufactured using the same machine.

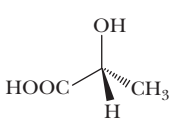
Enantiomers

6.15 (a), (c), and (d)

6.17



6.19 (a)



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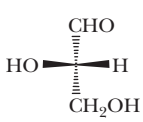

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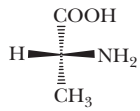

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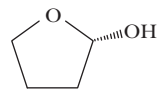
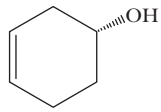


(e)



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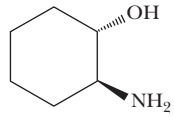
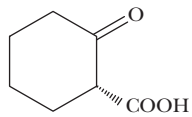
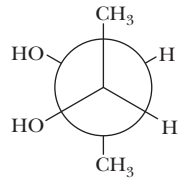


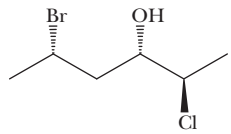
(g)



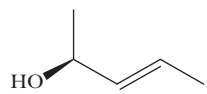
(h)



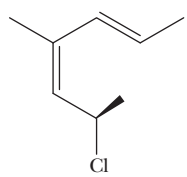
(i)



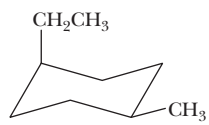
(j)



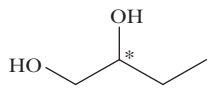
(k)



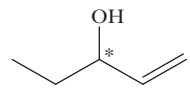
(l)



6.21 (b)



(c)

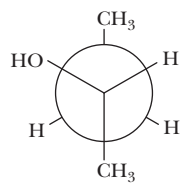


6.23 Structures (b), (c), (d), and (f) are identical to (a). Structures (e), (g), and (h) are mirror images of (a).

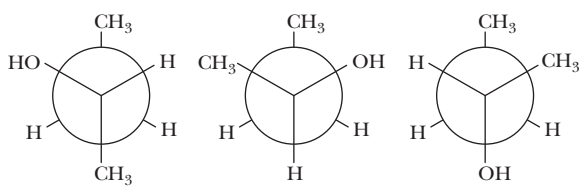
Designation of Configuration: The R,S Convention

6.25 (c) and (d)

6.27 (a) (*S*)-2-Butanol (b)



(c)



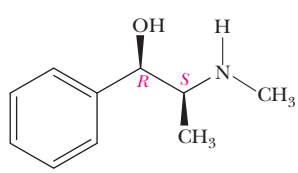
more stable more stable

(d) No

(e) Cannot be determined

Molecules with Two or More Stereocenters

6.29



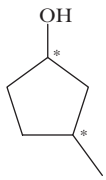
6.31

(a) $CH_3\overset{*}{C}HCHCOOH$ (HO, OH)

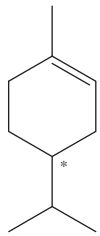
four stereoisomers

(b) $CH_2(COOH)-\overset{*}{C}H(COOH)-\overset{*}{C}H(OH)(COOH)$

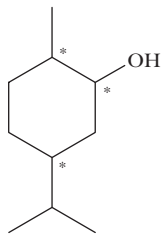
four stereoisomers

(c) 

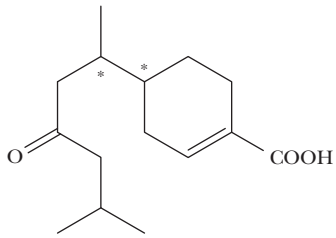
four stereoisomers

(d) 

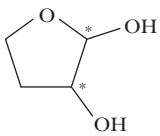
two stereoisomers

(e) 

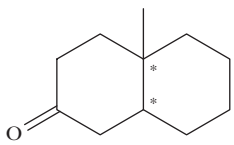
eight stereoisomers

(f) 

four stereoisomers

(g) 

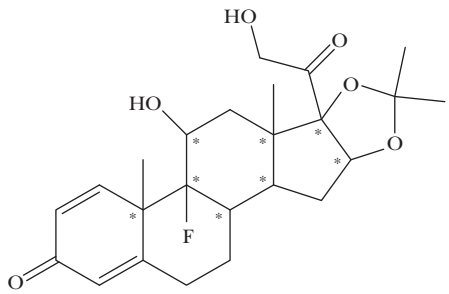
four stereoisomers

(h) 

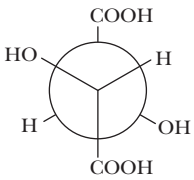
four stereoisomers

6.33 (a) Does not have any stereocenters

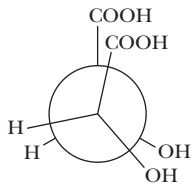
(b) Two stereoisomers

6.35 (a) 

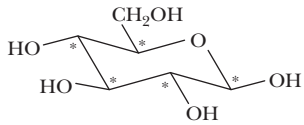
(b) 256

6.37 

most stable conformation



least stable conformation

6.39 (a) 

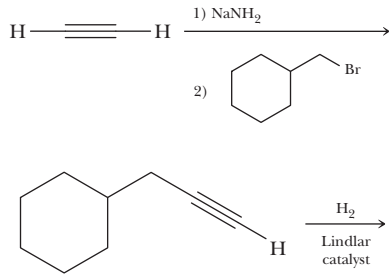
(b) 32

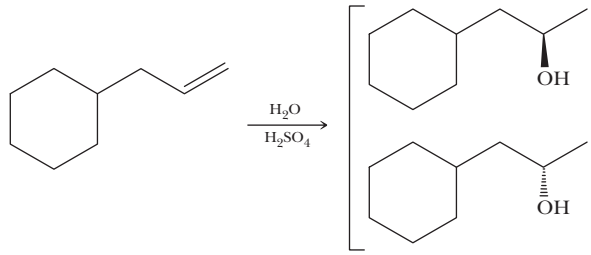
(c) 16

(d) Carbons 1 and 5 both have the *R* configuration.

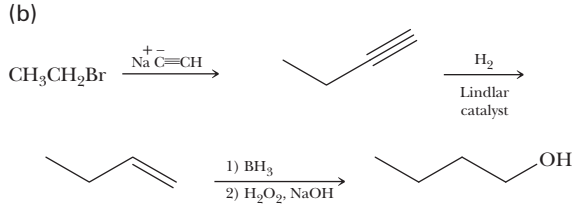
Chemical Transformations

6.41 (a)

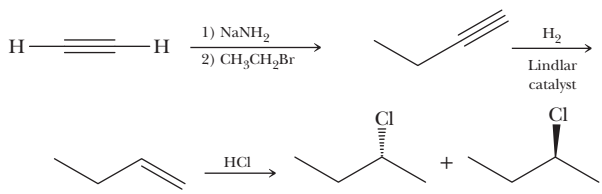




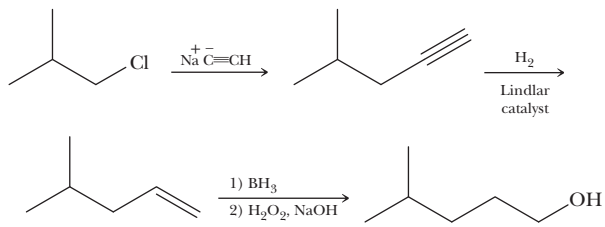
(b)



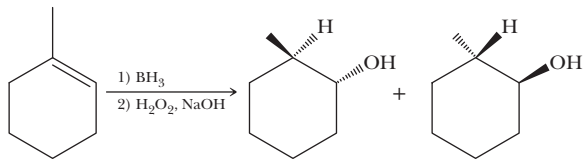
(c)



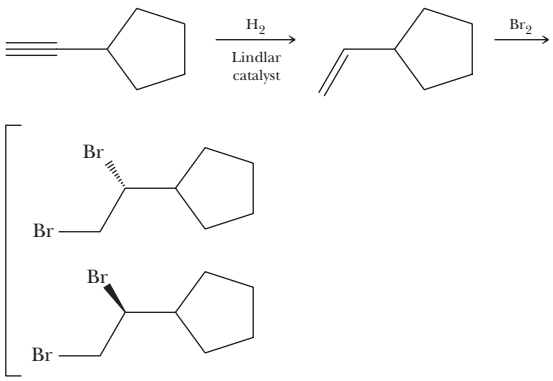
(d)



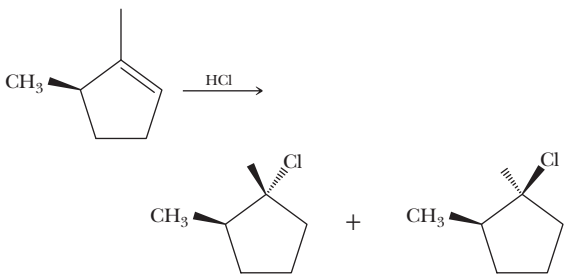
(e)



(f)



(g)



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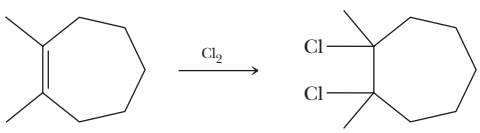
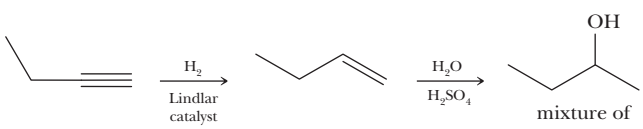


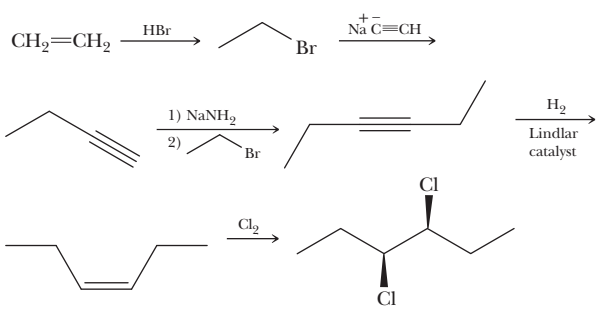
mixture of *trans* enantiomers

(i)

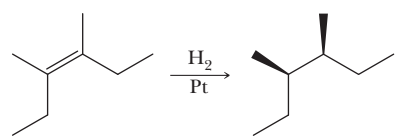


mixture of enantiomers

(j)



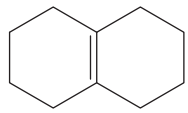
(k)



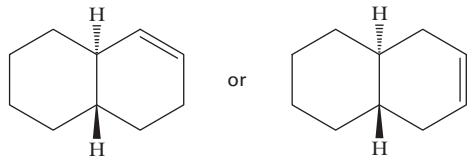
A mixture of enantiomers is not formed, because the product is meso.

Looking Ahead

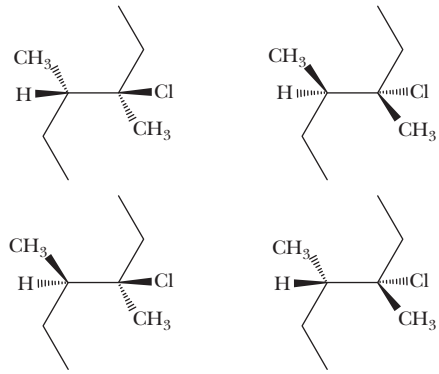
6.43 (a)



(b)



6.45



The reaction produces four different stereoisomers. If the goal of the synthesis is to selectively synthesize one of the four stereoisomers, this method is not very useful.

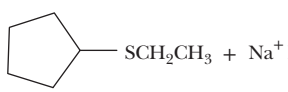
CHAPTER 7 Haloalkanes

Problems

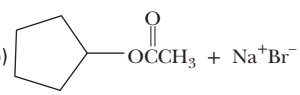
7.1 (a) 1-Chloro-3-methyl-2-butene
(b) 1-Bromo-1-methylcyclohexane
(c) (*S*)-1,2-Dichloropropane
(d) 2-Chloro-1,3-butadiene
(e) (*S*)-3-chloro-3-methyl-1-pentene

7.2 (a) Substitution
(b) Both substitution and elimination

7.3 (a)



(b)

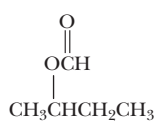


7.4 (a) S_N2
(b) Compound A is more able to undergo S_N2. Both compounds A and B have about the same reactivity toward S_N1.

7.5 (a)

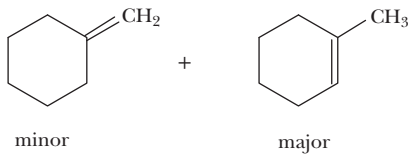
by S_N2

(b)



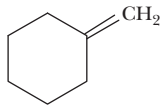
racemic mixture by S_N1

7.6 (a)

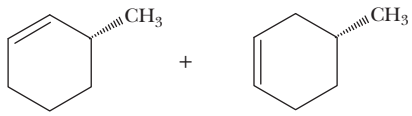


minor major

(b)



(c)

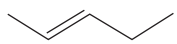


equal amounts

(d)

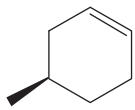
minor major

7.7 (a)



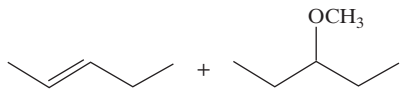
by E2

(b)



by E2

7.8 (a)



E2 and SN2 are likely to be competing mechanisms, with the elimination product being more favorable than the substitution product.

(b)

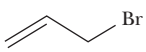
E2 and S_N2 are likely to be competing mechanisms.

End-of-Chapter Problems

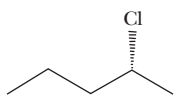
Nomenclature

7.9 (a) 1,1-Difluoroethene
(b) 3-Bromocyclopentene
(c) 2-Chloro-5-methylhexane
(d) 1,6-Dichlorohexane
(e) Dichlorodifluoromethane
(f) 3-Bromo-3-ethylpentane

7.11 (a)



(b)



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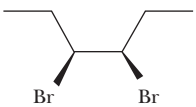
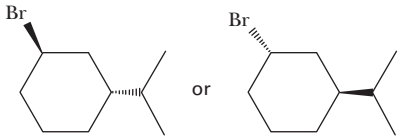
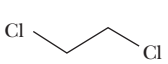


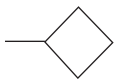
(d)



(e)



(f)



7.13 (b) and (c)

Synthesis of Alkyl Halides

7.15 (a) HCl (b) HI
(c) HCl (d) HBr

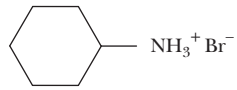
Nucleophilic Aliphatic Substitution

7.17 $CH_3NH_2 < CH_3CH_2OH < CH_3OH < H_2O$

7.19 (a) OH^- (b) OH^- (c) CH_3S^-

7.21 (a) $Na^+Cl^- + CH_3CH_2CH_2I$

(b)



(c) $Na^+Cl^- + CH_2{=}CHCH_2OCH_2CH_3$

7.23 (a) The haloalkane is 2°, acetate is a moderate nucleophile that is a weak base, and ethanol is a moderately ionizing solvent; these favor an S_N2 mechanism.

(b) The haloalkane is 2°, ethyl thiolate is a good nucleophile that is a weak base, and acetone is a weakly ionizing solvent; these favor an S_N2 mechanism.

(c) The haloalkane is 1°, and when combined with an excellent nucleophile such as iodide, the reaction will proceed by an S_N2 mechanism.

(d) Although the nucleophile is only a moderate nucleophile, the reaction can only proceed by S_N2 because the haloalkane is a methyl halide. Because methyl carbocations are extremely unstable, the reaction cannot proceed by an S_N1 mechanism.

(e) The haloalkane is 1°, and when combined with a good nucleophile such as methoxide, the reaction will proceed by an S_N2 mechanism. Although methoxide is also a good base, 1° haloalkanes will favor substitution over elimination.

(f) The haloalkane is 2°, methyl thiolate is a good nucleophile that is a weak base, and ethanol is a moderately ionizing solvent; these favor an S_N2 mechanism.

(g) Similar to (d), the amine is a moderate nucleophile. The haloalkane is 1°, which will not react by an S_N1 mechanism. Thus, the favored mechanism is S_N2.

(h) As with (d) and (g), the amine nucleophile (ammonia) is moderate. When combined with a 1° haloalkane, which cannot proceed by S_N1, the favored mechanism is S_N2.

7.25 (a) False. (b) False. (c) True.
(d) True. (e) False. (f) False.

7.27 (a) The 2° haloalkane forms a relatively stable carbocation, ethanol is a weak nucleophile, and the solvent (also ethanol) is moderately ionizing.

(b) The 3° haloalkane forms a very stable carbocation, methanol is a weak nucleophile, and the solvent (also methanol) is moderately ionizing.

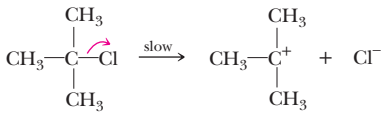
(c) The 3° haloalkane forms a very stable carbocation, acetic acid is a weak nucleophile, and the solvent (also acetic acid) is strongly ionizing.

(d) The 2° haloalkane forms a carbocation that is stabilized by resonance, methanol is a weak nucleophile, and the solvent (also methanol) is moderately ionizing.

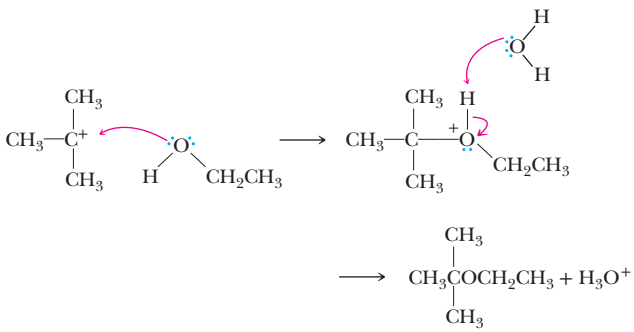
(e) The 2° haloalkane forms a carbocation that can rearrange (hydride shift) to form a 3° carbocation, and like (a), the nucleophile and solvent favor an S_N1 mechanism.

(f) The 2° haloalkane forms a carbocation that can rearrange (alkyl shift) to form a 3° carbocation, and like (c), the nucleophile and solvent favor an S_N1 mechanism.

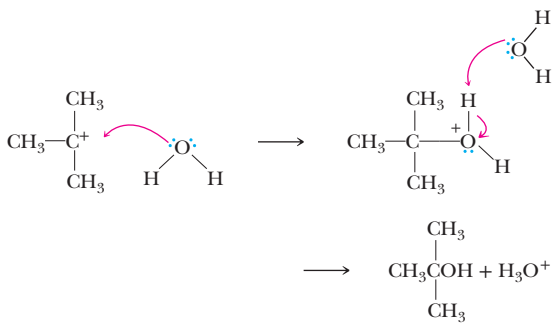
7.29 Both the S_N1 and E1 mechanisms involve the highly stable *tert*-butyl carbocation, which is generated in the first step of the reaction:



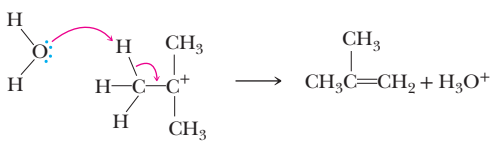
Attack of the carbocation by ethanol gives the ether product:

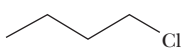
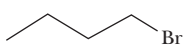


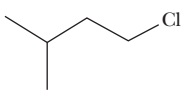
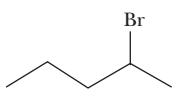
In a similar fashion, nucleophilic attack of the carbocation by water results in the alcohol:



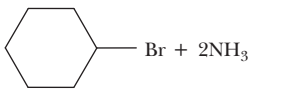
Deprotonation of the carbocation by the solvent (water or ethanol) gives the alkene:

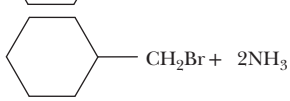


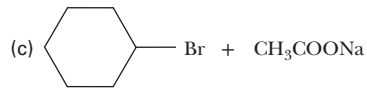
7.31 (a)  (b) 

(c)  (d) 

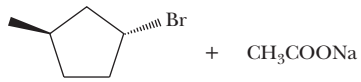
7.33 Haloalkenes fail to undergo S_N1 reactions because the alkenyl carbocations produced through ionization of the carbon–halogen bond are too unstable. They fail to undergo S_N2 reactions because the planar geometry of the alkene does not allow backside attack, and the electron-rich nature of the alkene does not attract nucleophiles.

7.35 (a) 

(b) 

(c) 

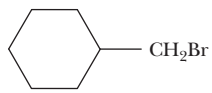
(d) 

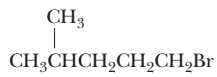
(e) 

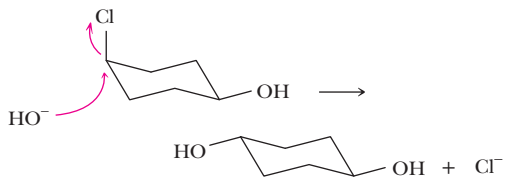
(f) $CH_3(CH_2)_2CH_2Br + NaOCH_2(CH_2)_2CH_3$

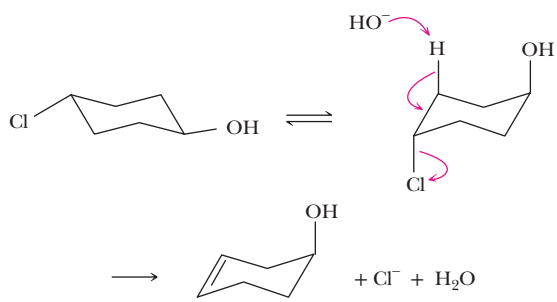
β-Eliminations

7.37 (c) and (d)

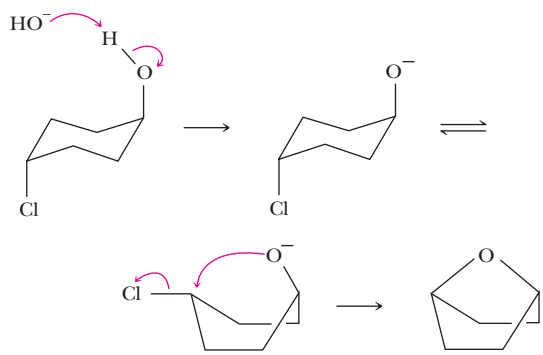
7.39 (a) 

(b) 

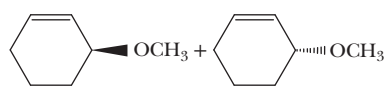
7.41 (a) 

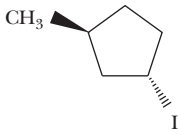
(b) 

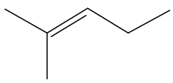
(c) With *trans*-4-chlorocyclohexanol, the nucleophilic atom is created by deprotonating the hydroxyl group. The resulting alkoxide is properly oriented to initiate a backside attack, whereas the alkoxide nucleophile generated from *cis*-4-chlorocyclohexanol is situated on the same side as the leaving group and cannot initiate a backside attack.

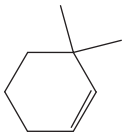


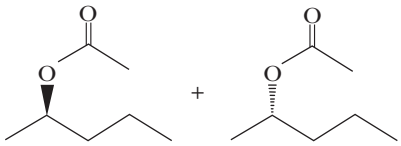
Synthesis and Predict the Product

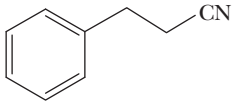
7.43 (a) S_N1 

(b) S_N2 

(c) E2 

(d) E2 

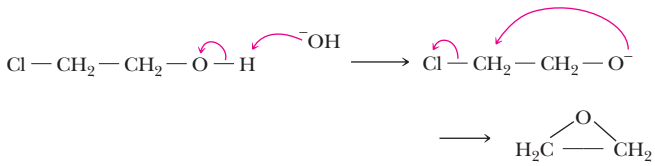
(e) S_N1 

(f) S_N2 

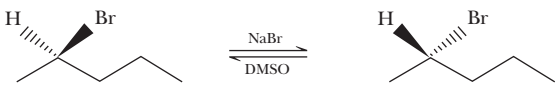
Looking Ahead

7.45 Reaction (a) gives the ether, while reaction (b) gives an alkene by an E2 reaction.

7.47



7.49 Over time, an equilibrium mixture consisting of equal amounts of both enantiomers is formed.



7.51 Although alkoxides are poor leaving groups, the opening of the highly strained three-membered ring is the driving force behind the opening of epoxides by nucleophiles.

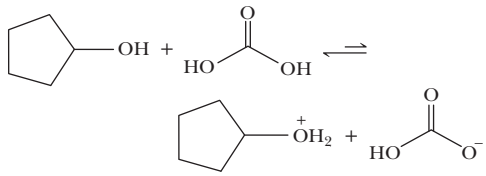
CHAPTER 8 Alcohols, Ethers, and Thiols

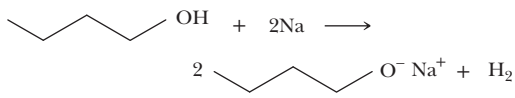
Problems

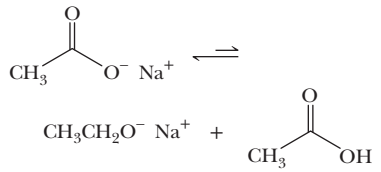
8.1 (a) 2-Heptanol
(b) 2,2-Dimethyl-1-propanol
(c) (1*R*,3*S*)-3-Isopropylcyclohexanol
(d) (2*R*,4*S*)-4-Cyclopentyl-2-pentanol

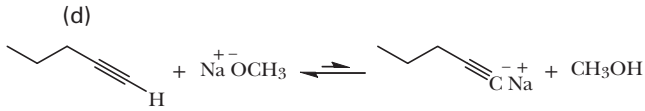
8.2 (a) primary (b) secondary
(c) primary (d) tertiary (e) tertiary

8.3 (a) *trans*-3-Penten-1-ol
(b) 2-Cyclopentenol
(c) (2*S*,3*R*)-1,2,3-Pentanetriol
(d) (1*R*,4*S*)-1,4-Cycloheptanediol

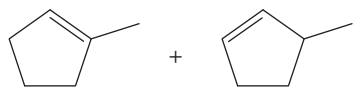
8.4 (a) 

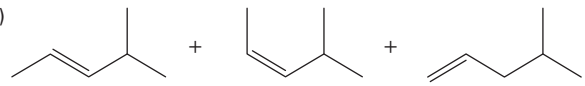
(b) 

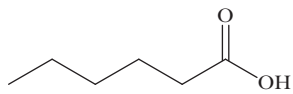
(c) 

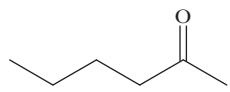
(d) 

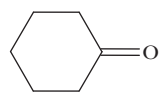
8.5 (a) 
major product minor product

(b) 
major product minor product

(c) 
major product minor product minor product

8.6 (a) 

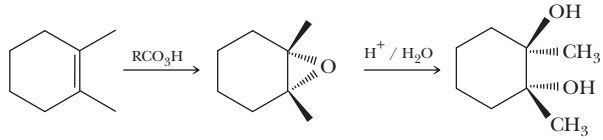
(b) 

(c) 

8.7 (a) 1-Ethoxy-2-methylpropane (Ethyl isobutyl ether)
(b) Methoxycyclopentane (Cyclopentyl methyl ether)
(c) (*E*)-1-Isopropoxypropene (Isopropyl (*E*)-1-propenyl ether)

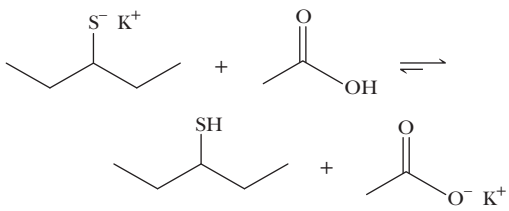
8.8 $CH_3OCH_2CH_2OCH_3 < CH_3OCH_2CH_2OH < HOCH_2CH_2OH$

8.9 

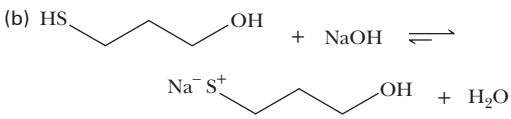
8.10 

8.11 (a) 3-Methyl-1-butanethiol (b) 3-Methyl-2-butanethiol (c) Cyclopentanethiol

8.12 (a)



(b)



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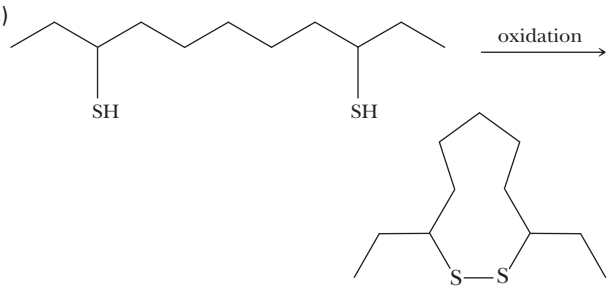

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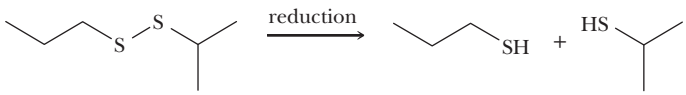


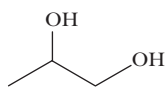
End-of-Chapter Problems

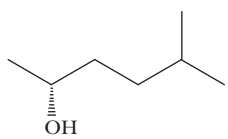
Structure and Nomenclature

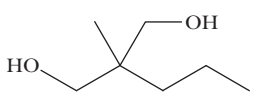
8.13 (a) 3° (b) 3° (c) 1° (d) 3° (e) 2° (f) 2° (g) 3° (h) 2°

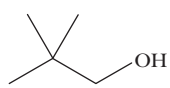
8.15

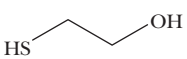
(a) 

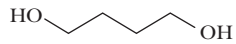
(b) 

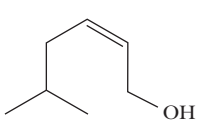
(c) 

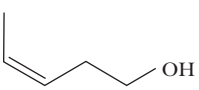
(d) 

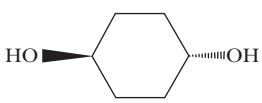
(e) 

(f) 

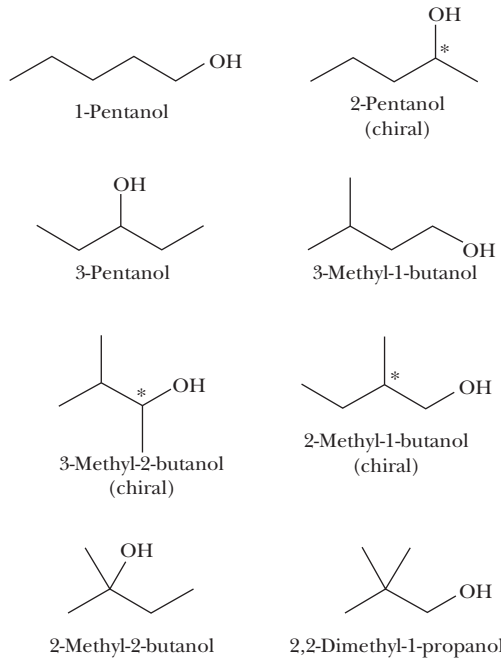
(g) 

(h) 

(i) 

(j) 

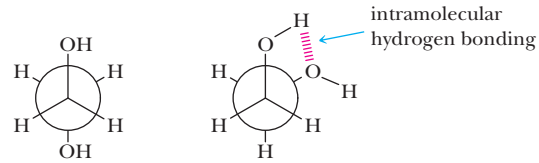
8.17



Physical Properties

8.19 $CH_3CH_2CH_3 < CH_3OCH_3 < CH_3CH_2OH < CH_3COOH$

8.21



Intramolecular hydrogen bonding can occur between the hydroxyl groups. The strength of the hydrogen bond is greater than 4.2 kJ/mol, so the net result is that the conformation with the larger groups closest to each other is more stable.

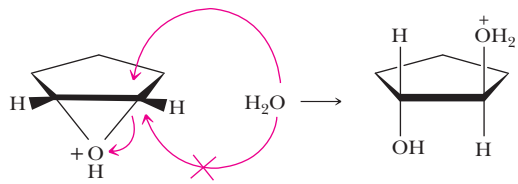
8.23 (a) CH_3OH (b) $CH_3\overset{\overset{O}{\|}}{C}CH_3$ (c) NaCl (d) $CH_3CH_2CH_2OH$ (e) $CH_3CH_2\overset{\overset{OH}{|}}{C}HCH_2CH_3$

8.25 (a) CH_3CH_2OH (b) CH_3CH_2OH (c) $CH_3\overset{\overset{O}{\|}}{C}CH_3$ (d) $CH_3CH_2OCH_2CH_3$

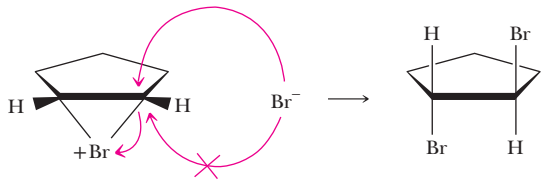
Synthesis of Alcohols

8.27 The two reactions are stereoselective and result in *trans* products because they both involve an intermediate consisting of a three-membered ring. To open the ring, the nucleophile preferentially attacks from the least-hindered side, which is the side opposite (anti) to that of the three-membered ring. The key ring-opening steps are shown.

Acid-catalyzed hydrolysis of epoxide:



Bromination:



cyclic brominium ion

Acidity of Alcohols and Thiols

8.29 $CH_3CH_2CH_2OH < CH_3CH_2CH_2SH < CH_3CH_2\overset{O}{\overset{\|}{C}}OH$

8.31 (a) $CH_3CH_2O^- + HCl \rightleftharpoons CH_3CH_2OH + Cl^-$

stronger base; stronger acid; weaker acid; weaker base

The equilibrium lies far to the right.

(b) $CH_3\overset{O}{\overset{\|}{C}}OH + CH_3CH_2O^- \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}O^- + CH_3CH_2OH$

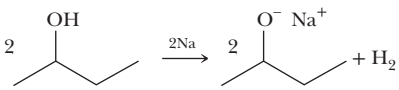
stronger acid; stronger base; weaker base; weaker acid

The equilibrium lies far to the right.

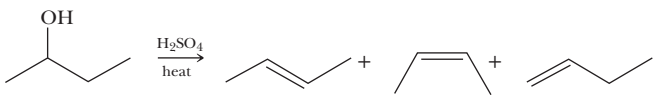
Reactions of Alcohols

8.33 Both cyclohexanol and cyclohexene are colorless. However, cyclohexene will decolorize an orange-red solution of bromine dissolved in CCl_4 (the solvent), while cyclohexanol does not react with bromine.

8.35 (a)

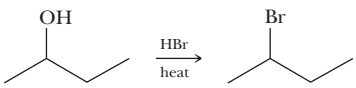


(b)

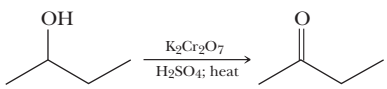


major product

(c)

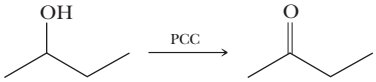


(d)

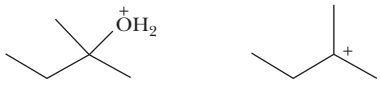


(e)

(f)

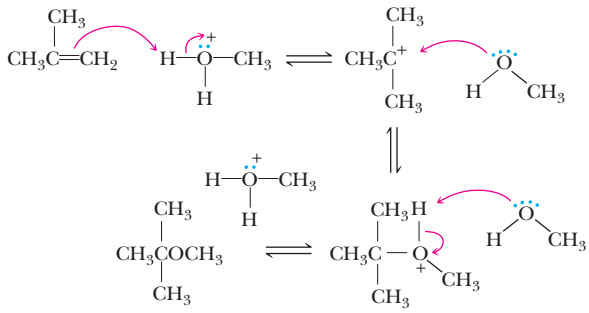


8.37 The reaction most likely proceeds by an S_N1 mechanism. Intermediates formed are:



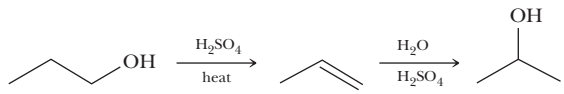
Oxonium ion intermediate; Carbocation intermediate

8.39



Syntheses

8.41 (a)



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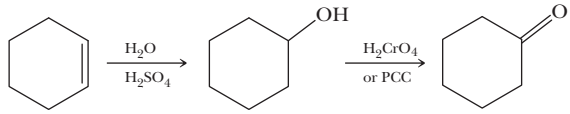

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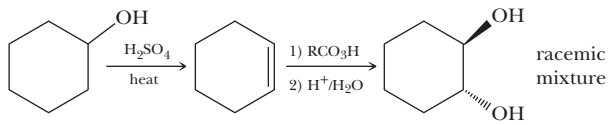

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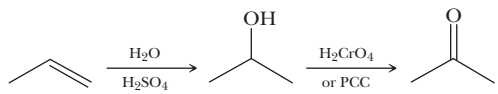
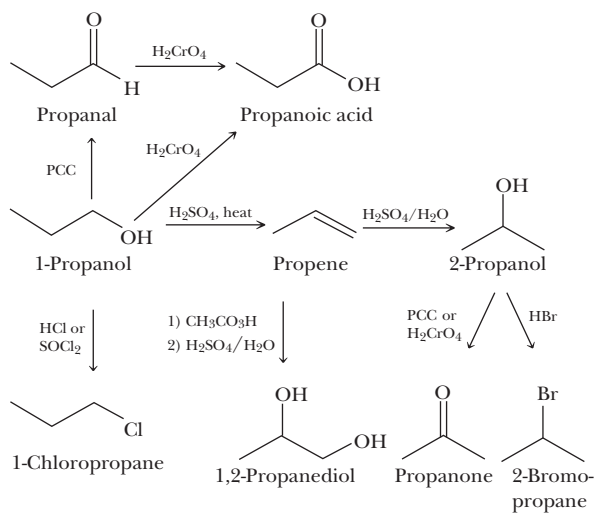
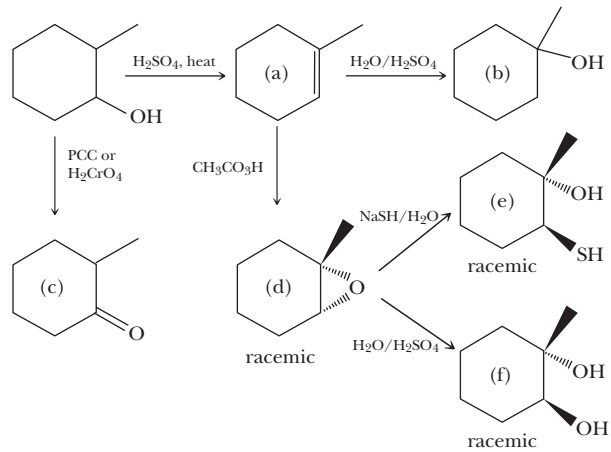


8.43



8.45



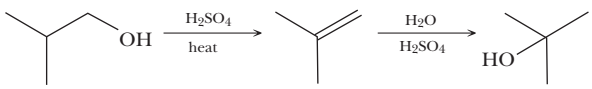
8.47 (a) A peroxycarboxylic acid, such as CH_3CO_3H, will convert the alkene into an epoxide.

(b) There are two stereocenters, giving rise to a maximum of $2^2 = 4$ stereoisomers. However, only two are formed due to the stereoselectivity of the epoxidation reaction.

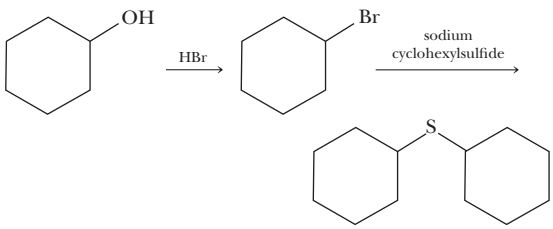
Chemical Transformations

8.49

(a)



(b)



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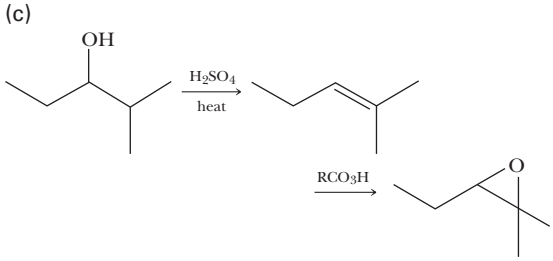

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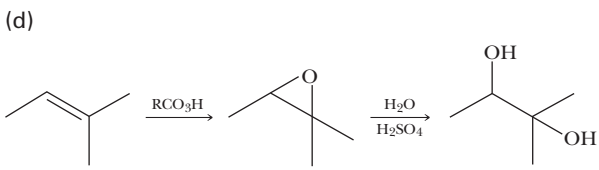

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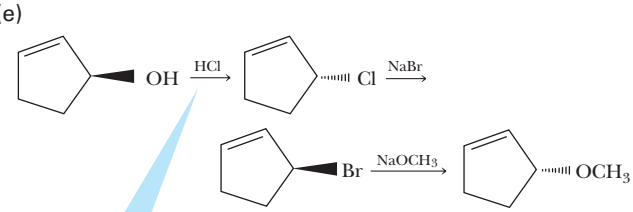
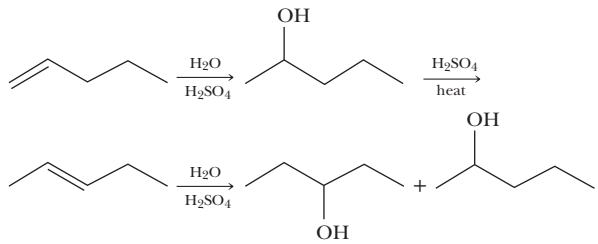


this competes with S_N1. In Chapter 13, we will encounter $SOCl_2$, a reagent that will give more of the desired S_N2 product.

(f)



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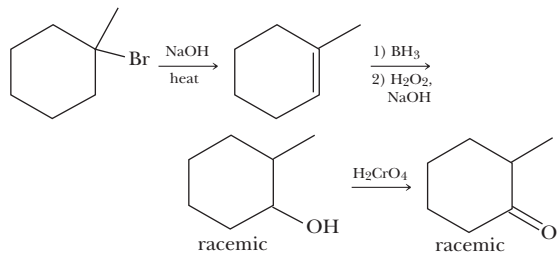

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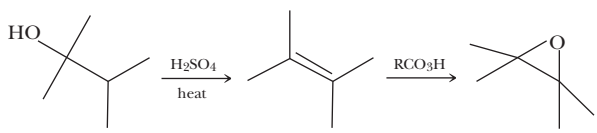

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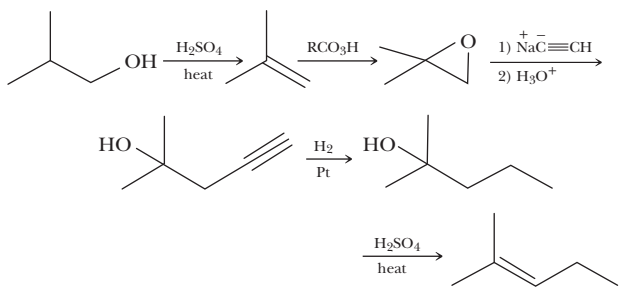

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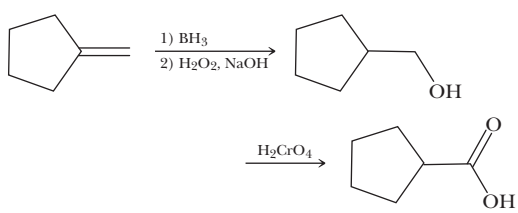
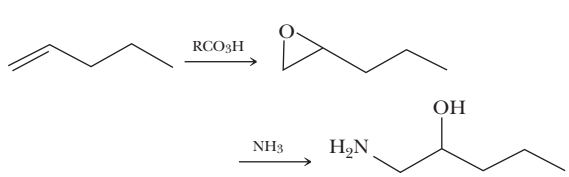


(k)



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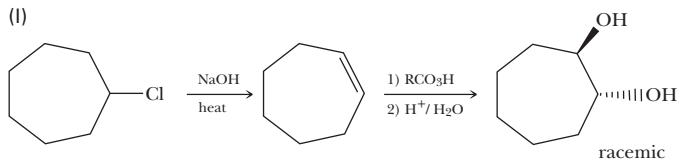

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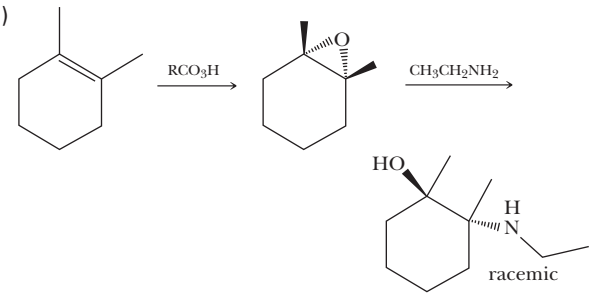

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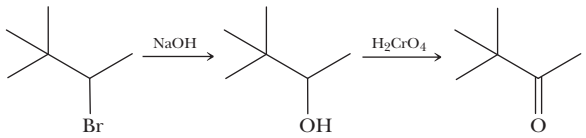
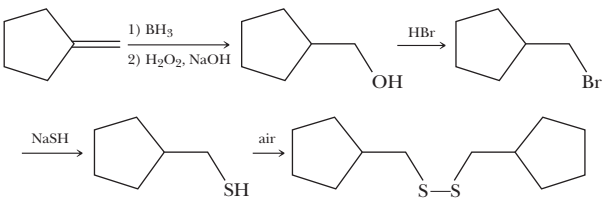


(o)

(p)



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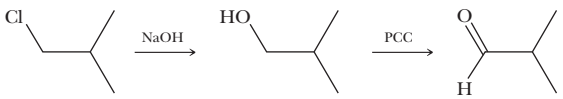

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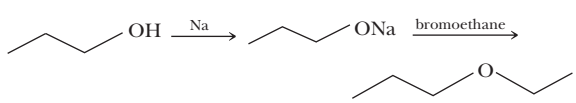

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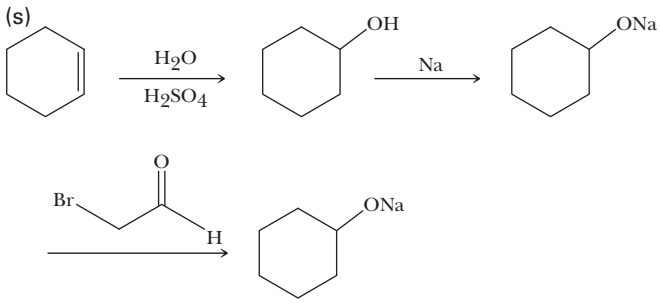
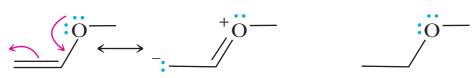


Looking Ahead

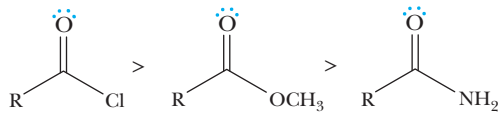
8.51



Ethyl vinyl ether Ethyl methyl ether

As a result of resonance, the oxygen of methyl vinyl ether carries a partial positive charge, which makes it less reactive toward an electrophile. The oxygen of ethyl methyl ether is also less basic than the oxygen of ethyl methyl ether.

8.53



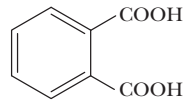
CHAPTER 9 Benzene and Its Derivatives

Problems

9.1 (a), (c), and (d)

9.2 (a) 2-Phenyl-2-propanol
(b) (*E*)-3,4-Diphenyl-3-hexene
(c) 3-Methylbenzoic acid or *m*-methylbenzoic acid
(d) 3-Bromo-5-chlorobenzaldehyde
(e) 4-chloro-3-ethylanisole

9.3 (a)



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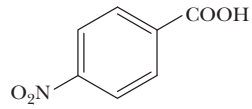

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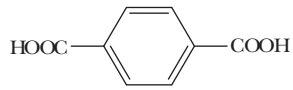

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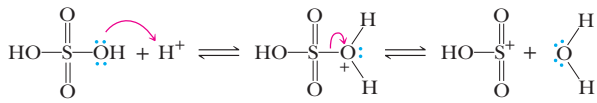

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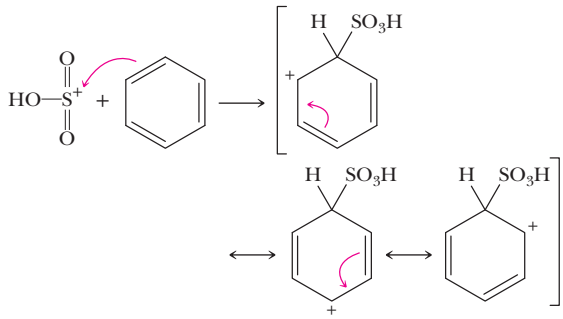

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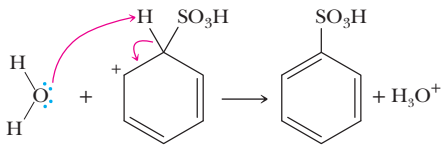
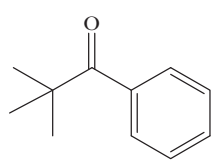


9.5 (a)



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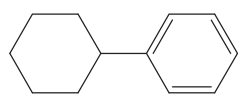

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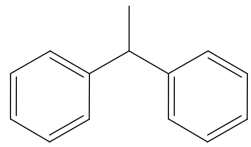

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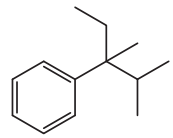

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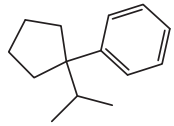

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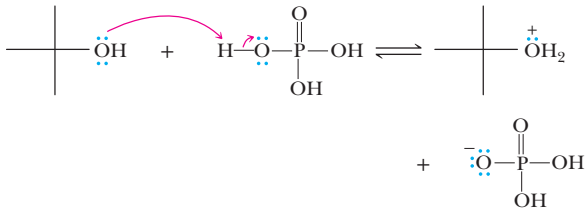

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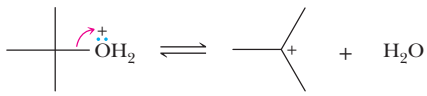

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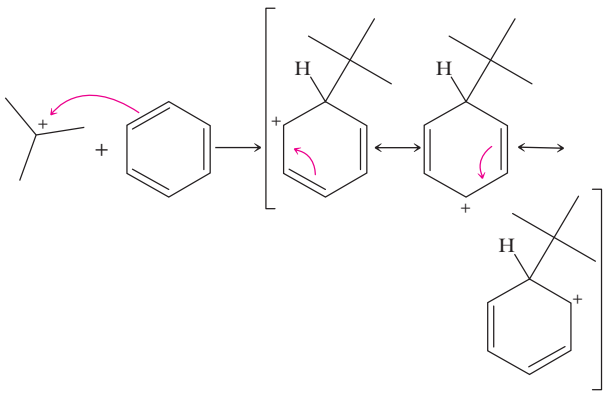

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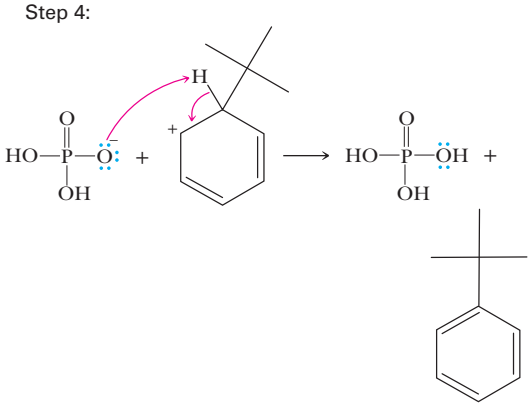
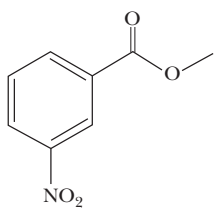


9.7 (a)



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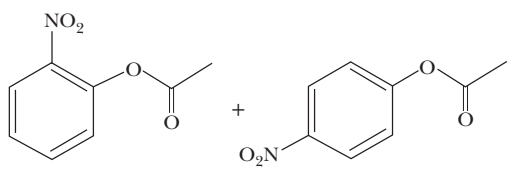
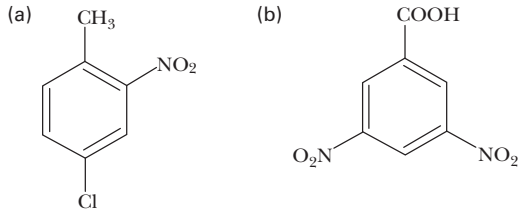


9.8 If the electrophile is added ortho or para, it is possible to draw a contributing structure that places the positive charge directly adjacent to the partially positive carbon atom of the carbonyl group. This interaction destabilizes the carbocation, which in turn disfavors ortho-para attack of the electrophile.

On the other hand, if the electrophile is added meta, no contributing structure places the carbocation directly adjacent to the carbon atom of the carbonyl group. Because there are no destabilizing interactions, meta attack is more favorable.

9.9 (a) (b)



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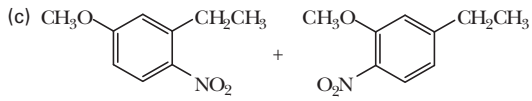

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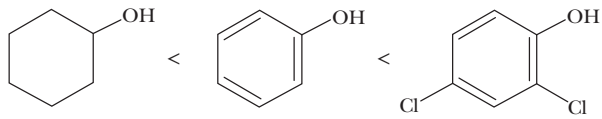


End-of-Chapter Problems

Aromaticity

9.11 (c), (d), (e), (g), (j), (k), (l)

Nomenclature and Structural Formulas

9.13 (a) 1-Chloro-4-nitrobenzene (*p*-Chloronitrobenzene)

(b) 1-Bromo-2-methylbenzene or 2-bromotoluene or *o*-bromotoluene

(c) 3-Phenyl-1-propanol

(d) 2-Phenyl-3-buten-2-ol

(e) 3-Nitrobenzoic acid or *m*-nitrobenzoic acid

(f) 1-Phenylcyclohexanol

(g) (*E*)-1,2-Diphenylethene or *trans*-1,2-diphenylethene

(h) 2,4-Dichlorotoluene

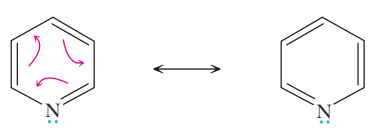
(i) 4-Bromo-2-chloro-1-ethylbenzene

(j) 1-Fluoro-3-isopropyl-5-vinylbenzene or 3-fluoro-5-isopropylstyrene

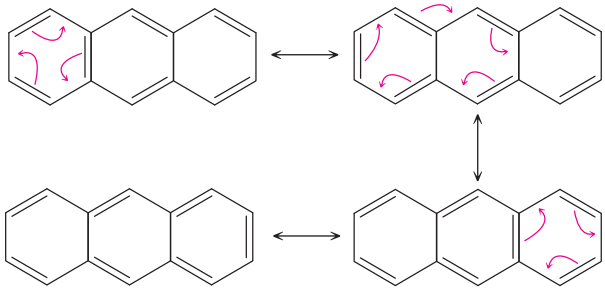
(k) 1-Amino-2-chloro-4-ethylbenzene or 2-chloro-4-ethylaniline

(l) 1-Methoxy-4-vinylbenzene or *p*-methoxystyrene

9.15

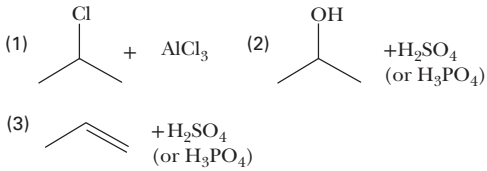


9.17



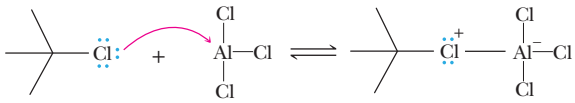
Electrophilic Aromatic Substitution: Monosubstitution

9.19



9.21

Step 1:



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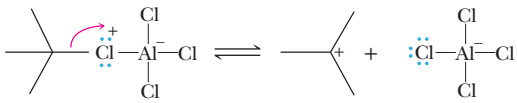

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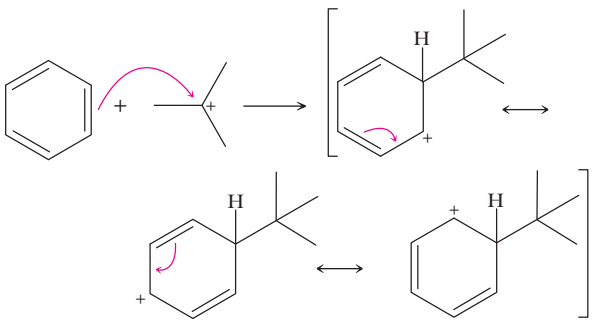

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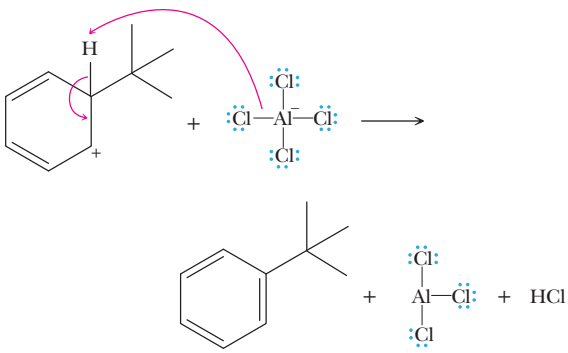
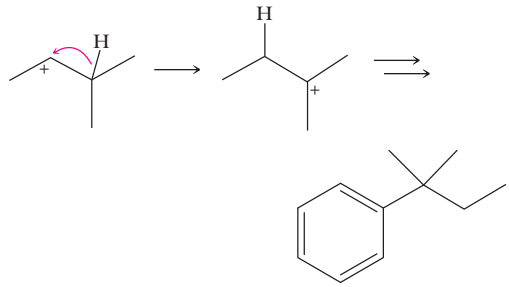


9.23 The carbocations formed in these reactions undergo rearrangement.

(a)



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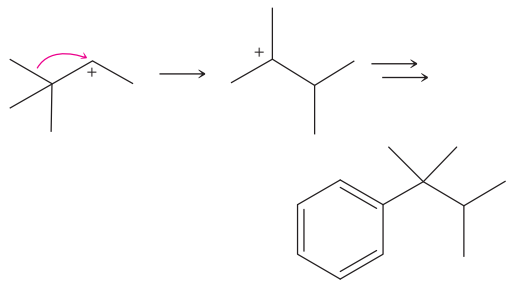

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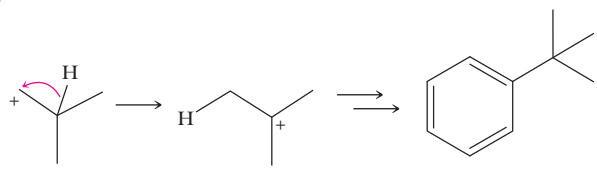
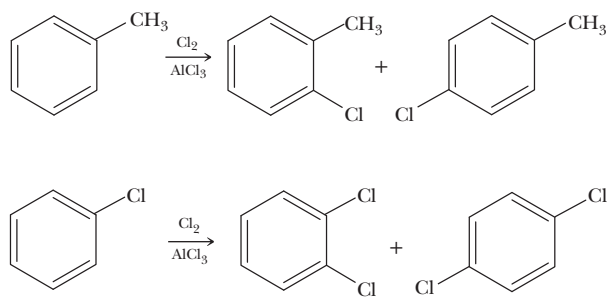


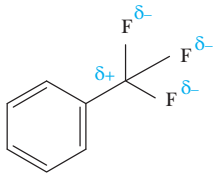
Electrophilic Aromatic Substitution: Substituent Effects

9.25 One product is formed from *p*-xylene, but *m*-xylene forms two products.

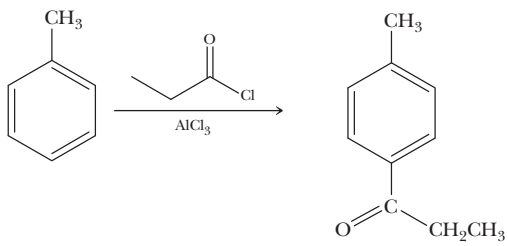
9.27 Toluene will react faster than chlorobenzene. Both the methyl and chlorine substituents are ortho-para directors, but the electronegative chlorine deactivates the benzene ring toward electrophilic attack. Because the slow step of the reaction is the attack of the electrophile, a deactivated benzene ring reacts more slowly.



9.29 The trifluoromethyl group is a strong electron-withdrawing group and therefore a meta director. The three fluorine atoms make the carbon atom of the trifluoromethyl group, which is bonded directly to the ring, highly δ+.



9.31 (a)



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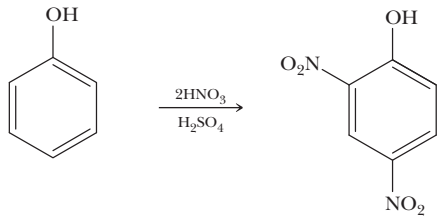
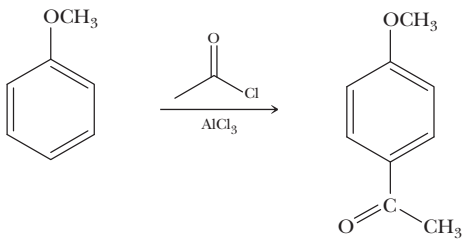


(c)



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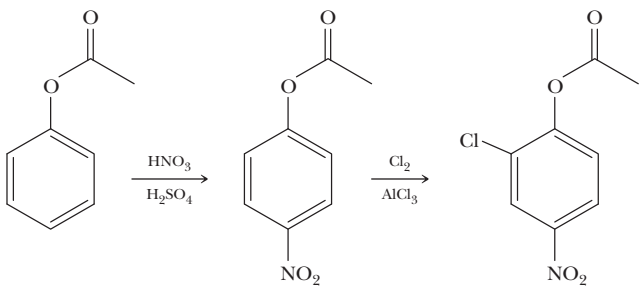

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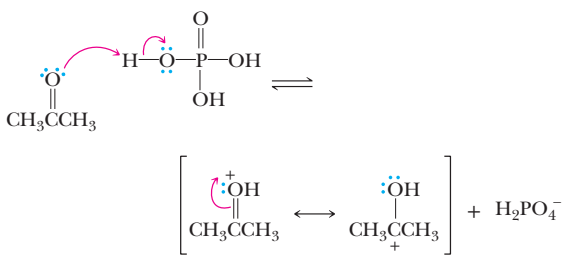

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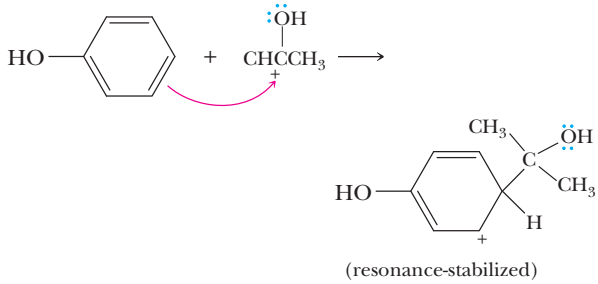

(resonance-stabilized)

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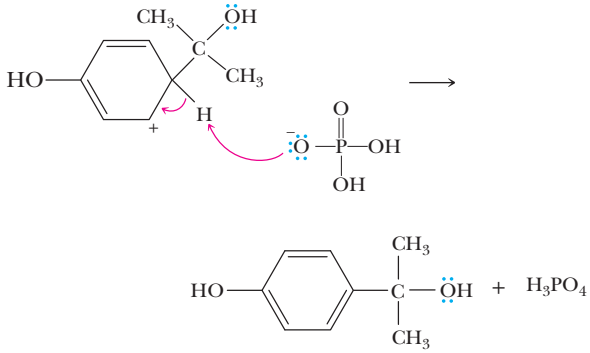

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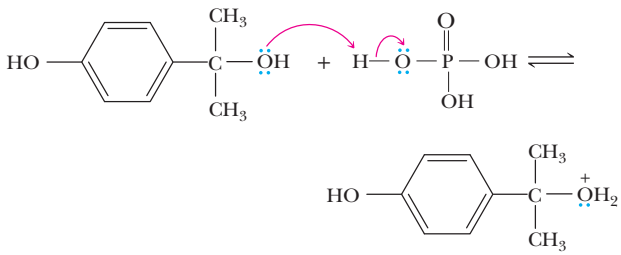

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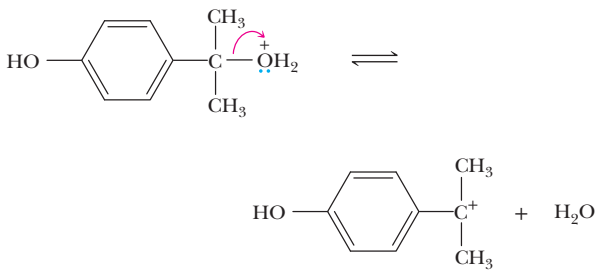

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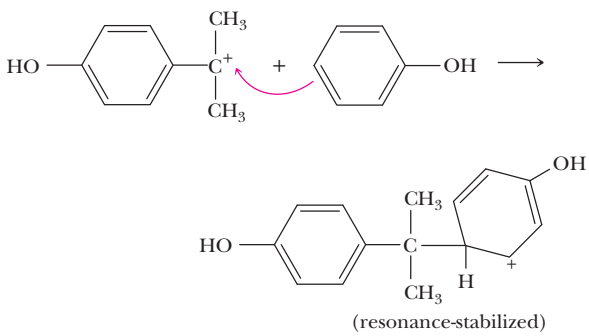

(resonance-stabilized)

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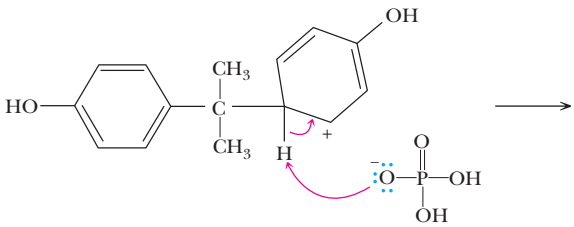
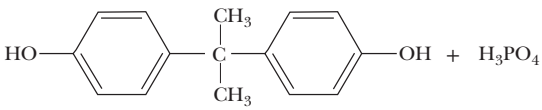
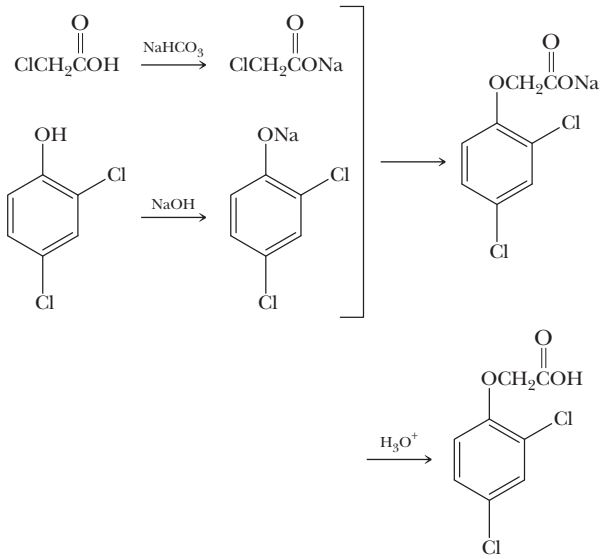




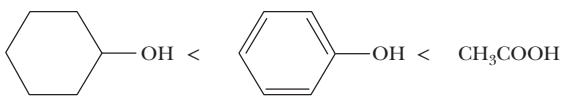
9.35



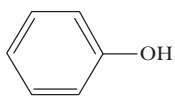
Acidity of Phenols

9.37

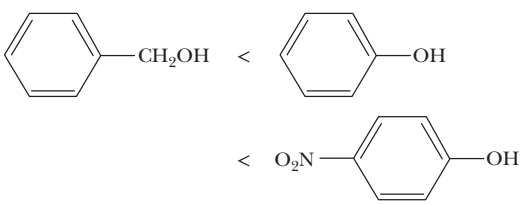
(a)



(b) H_2O < $NaHCO_3$ <



(c)



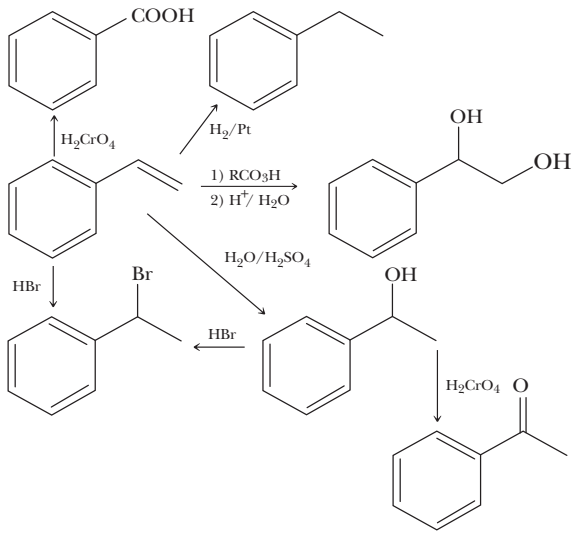
9.39 The gas formed is carbon dioxide, which arises from the decomposition of carbonic acid.

$$H_2CO_3 \longrightarrow CO_2 + H_2O$$

Carbonic acid ($pK_a = 6.36$) is formed when HCO_3^- acts as a base. A carboxylic acid is a stronger acid than carbonic acid, so the bicarbonate ion is a strong enough base to deprotonate a carboxylic acid. However, because a phenol is a weaker acid than carbonic acid, bicarbonate is not a strong enough base to deprotonate phenol.

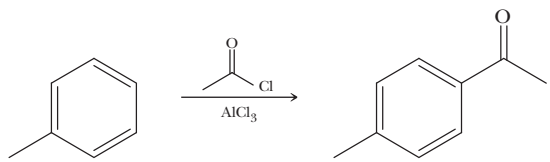
Syntheses

9.41



9.43

(a)



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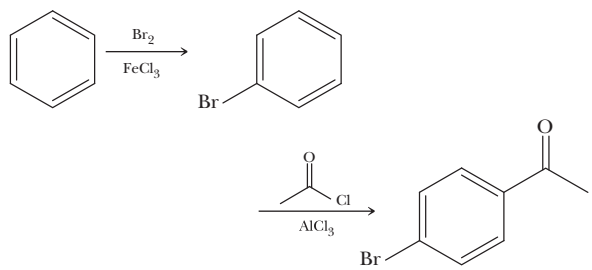

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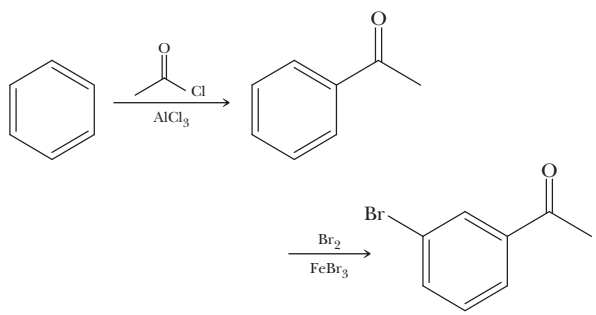

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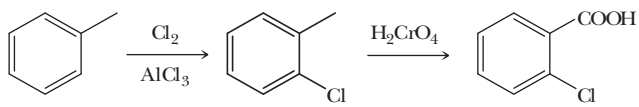
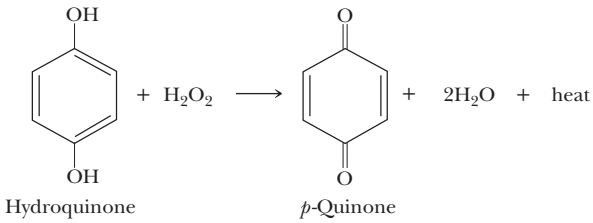
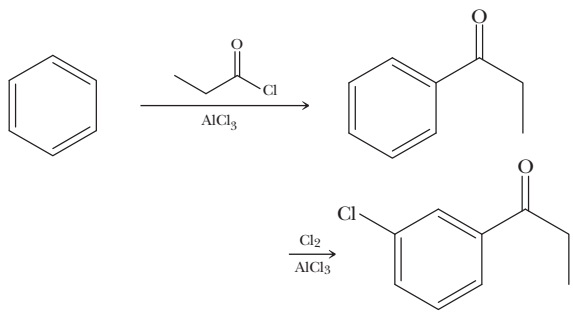


9.45 (a)



(b) Two hydrogen atoms have been removed from hydroquinone.

9.47

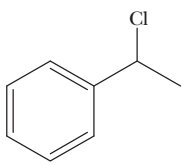


Looking Ahead

9.49 None of these compounds can be made *directly*.

9.51 There are a couple of reasons why these arenes do not undergo electrophilic aromatic substitution when $AlCl_3$ is used. First, $AlCl_3$ decomposes in the presence of protic acids (ionizable hydrogens) to form HCl. Second, $AlCl_3$ (a Lewis acid) reacts with —OH, —SH, and —NH_2 groups, which are Lewis bases. These two reactions destroy the catalyst.

9.53



CHAPTER 10 Amines

Problems

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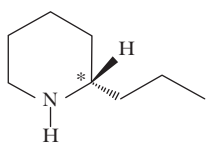

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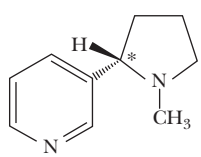

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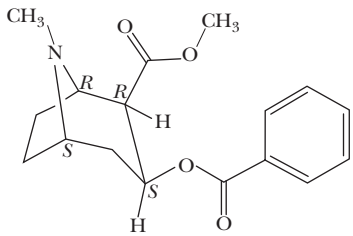

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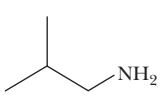

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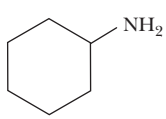

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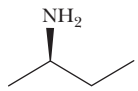

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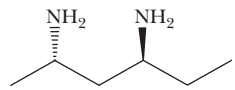
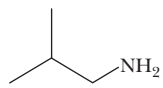


10.3 (a)



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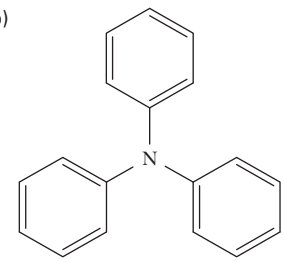

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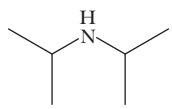

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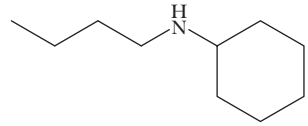
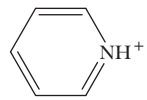


10.4 The NH group acts as a hydrogen-bond acceptor and donor. No intermolecular hydrogen bonding is possible with the ether.

10.5 Left

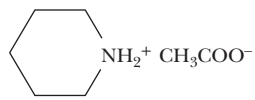
10.6 (a)

(b)



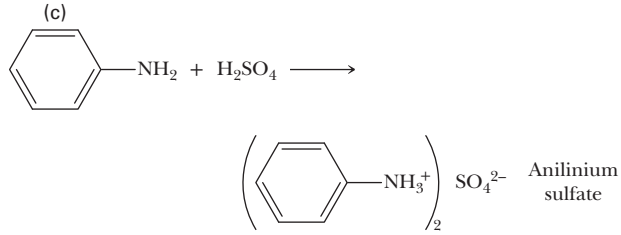
10.7 (a) $(CH_3CH_2)_3NH^+Cl^-$ Triethylammonium chloride

(b)



Piperidinium acetate

(c)

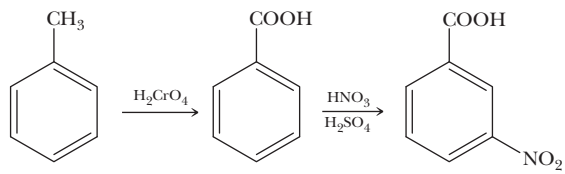


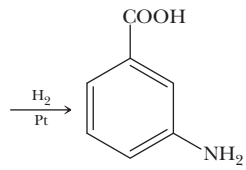
Anilinium sulfate

10.8 (a) CH_3CHCOH with O above, NH_3^+ below

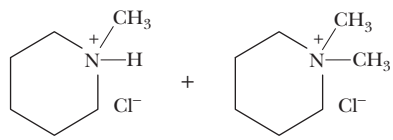
(b) CH_3CHCO^- with O above, NH_2 below

10.9



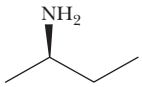


10.10

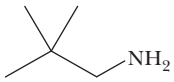


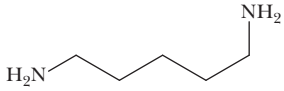
End-of-Chapter Problems

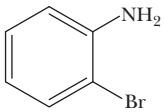
Structure and Nomenclature

10.11 (a) 

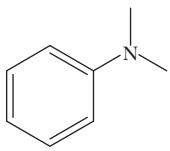
(b) $CH_3(CH_2)_6CH_2NH_2$

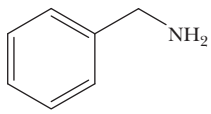
(c) 

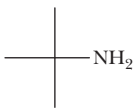
(d) 

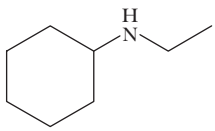
(e) 

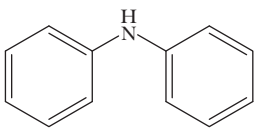
(f) $(CH_3CH_2CH_2CH_2)_3N$

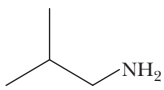
(g) 

(h) 

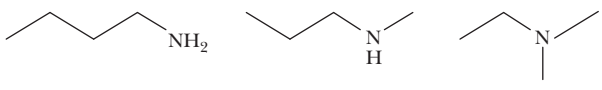
(i) 

(j) 

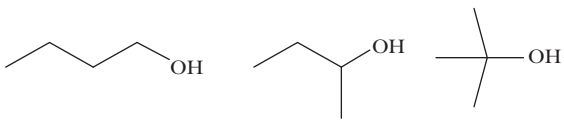
(k) 

(l) 

10.13 Amines are classified by the number of carbon substituents bonded to the nitrogen atom, whereas alcohols are classified by the number of carbon substituents bonded to the carbon bearing the —OH group.



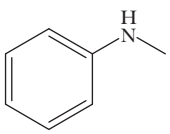
1° amine 2° amine 3° amine

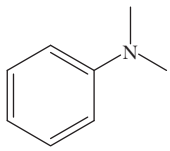


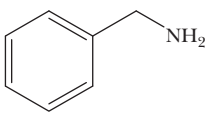
1° alcohol 2° alcohol 3° alcohol

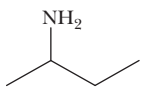
10.15 (a) Both amino groups are secondary.

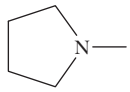
(b) Both compounds contain the same basic framework and have the same configuration at the stereocenter. Differences are the *tert*-butyl and —CH_2OH groups in (*R*)-albuterol versus the methyl and —OH groups in (*R*)-epinephrine, respectively.

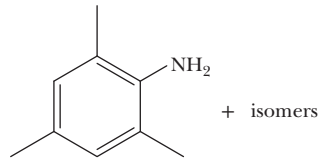
10.17 (a) 

(b) 

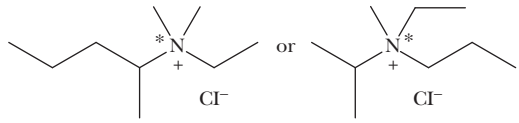
(c) 

(d) 

(e) 

(f) 

+ isomers

(g) 

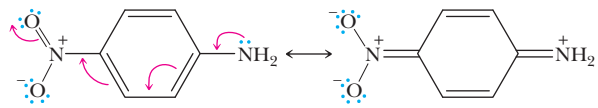
Physical Properties

10.19 1-Butanol has a higher boiling point because an O—H—O hydrogen bond is stronger than an N—H—N hydrogen bond.

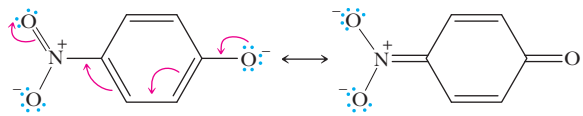
Basicity of Amines

10.21 Nitrogen is less electronegative than oxygen.

10.23 The nitro group is an electron-withdrawing group. In addition, it is able to stabilize the lone pair of electrons on the nitrogen atom in 4-nitroaniline by resonance.

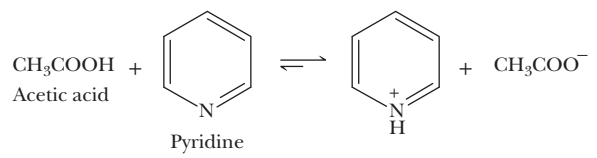


Likewise, the nitro group can stabilize the conjugate base of 4-nitrophenol, 4-nitrophenoxide, by both induction and resonance.



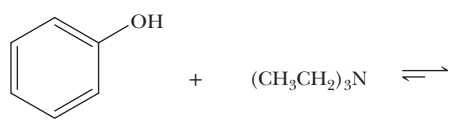
10.25

(a)

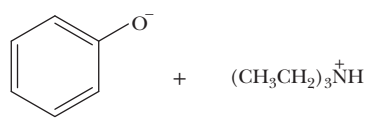


Acetic acid — Pyridine — stronger acid — stronger base — weaker acid — weaker base

(b)

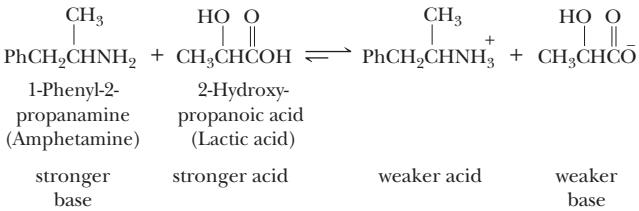


Phenol — Triethylamine — stronger acid — stronger base



weaker base — weaker acid

(c)



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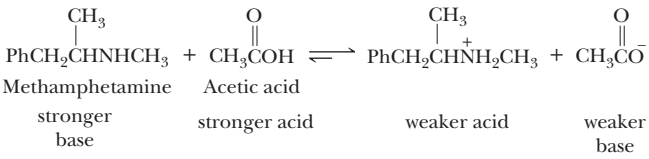
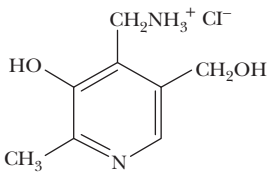


10.27 1:2500

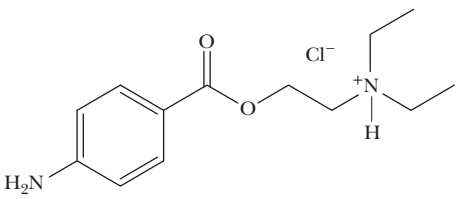
10.29 (a) The primary aliphatic amine.

(b)



10.31 (a) The tertiary aliphatic amine.

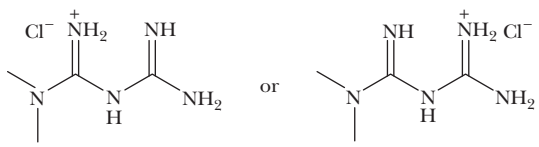
(b)



(c) Procaine is not chiral. A solution of Novocaine® would be optically inactive.

10.33 First, dissolve the reaction mixture in an organic solvent such as diethyl ether. The ethereal solution can be extracted with an aqueous acid, such as HCl, which reacts with aniline, a base, to form a water-soluble salt. Thus, the ether layer contains nitrobenzene while the aqueous layer contains the anilinium salt. After separating the two layers, the acidic aqueous layer can be basified with NaOH to deprotonate the anilinium ion. Extraction of the basified aqueous layer with diethyl ether, followed by evaporation of the ether, allows aniline to be isolated.

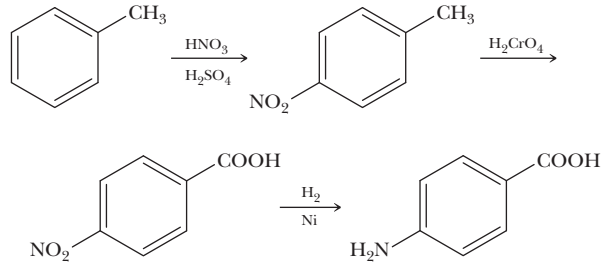
10.35 (a)



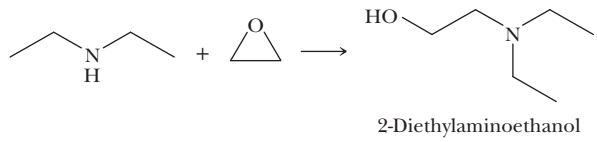
(b) As the hydrochloride salt of an amine, Glucophage is ionic and is soluble in water. It will also be soluble in blood plasma; the pK_a of the guanidinium group is much higher than the pH of blood (7.4), so the guanidinium nitrogen will be protonated and carry a positive charge. Because Glucophage is ionic, it is insoluble in solvents of much lower polarity, such as diethyl ether or dichloromethane.

Synthesis

10.37

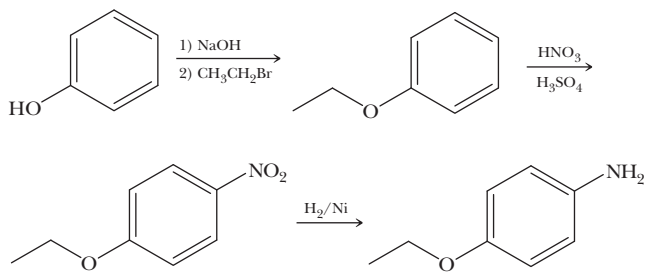


10.39

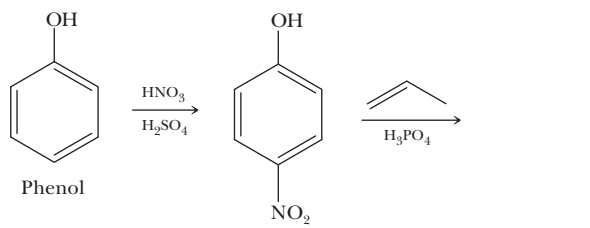


2-Diethylaminoethanol

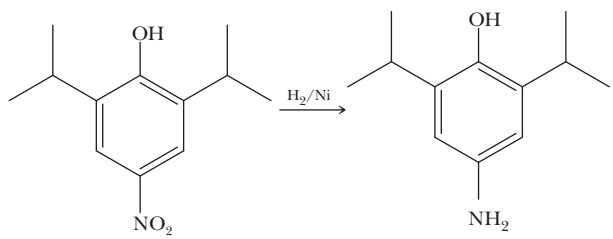
10.41



10.43



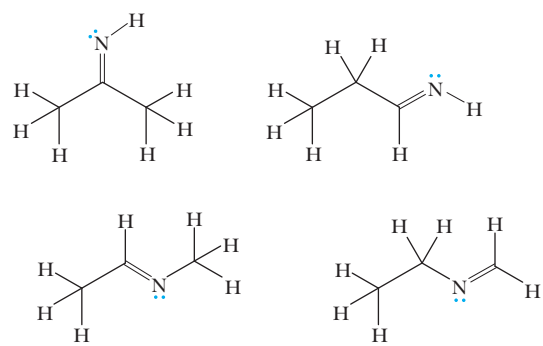
Phenol



Looking Ahead

10.45 All of the nitrogen atoms are sp^2.

10.47



CHAPTER 11 Infrared Spectroscopy

Problems

11.1 The energy of red light (680 nm) is 176 kJ/mol (42.1 kcal/mol) and is higher than the energy from infrared radiation of 2500 nm (47.7 kJ/mol or 11.4 kcal/mol).

11.2 Carboxyl group

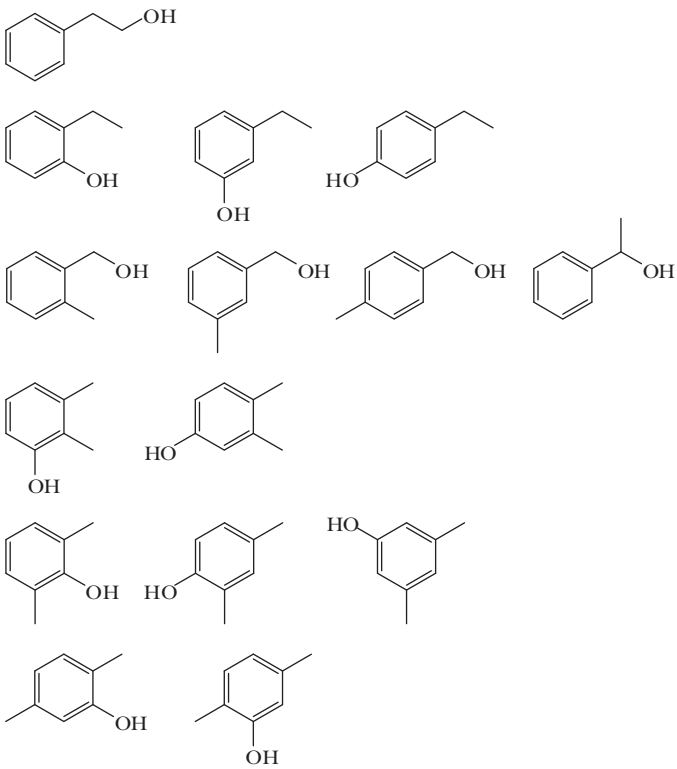
11.3 Only propanoic acid will have a strong, broad OH absorption between 3200 and 3500 cm^{-1}.

11.4 The wavenumber is directly related to the energy of the infrared radiation required to stretch the bond. Bonds that require more energy to stretch are stronger bonds.

11.5 Cyclohexene has one ring and one π bond, so it has an IHD of two.

11.6 Each index of hydrogen deficiency could be a ring or a π bond. Niacin contains one ring and four π bonds.

11.7 The $C_8H_{10}O$ compounds that would have the same spectrum as the C_7H_8O compounds are shown below. IR spectroscopy only provides functional group information and is not effective for the determination of the actual structure of a compound.



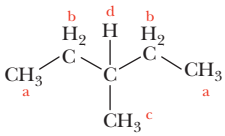
11.8 (a) and (b)

11.9 (a) 3-Methylpentane has four sets of equivalent hydrogens. The number of hydrogens in each set are 6, 4, 3, and 1, which are respectively labeled a, b, c, and d.

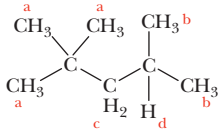
(b) 2,2,4-Trimethylpentane has four sets of equivalent hydrogens. The number of hydrogens in each set are 9, 6, 2, and 1, which are respectively labeled a, b, c, and d.

(c) 1,4-Dichloro-2,5-dimethylbenzene has two sets of equivalent hydrogens. The number of hydrogens in each set are 6 and 2, which are respectively labeled a and b.

(a)



(b)



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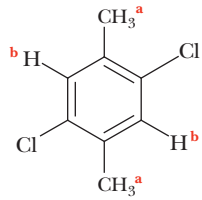
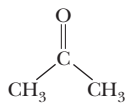
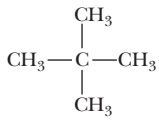


11.10 (a)

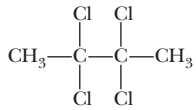


(b)

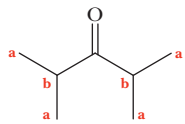
(c)



(d)



11.11 12 *a* hydrogens and 2 *b* hydrogens.

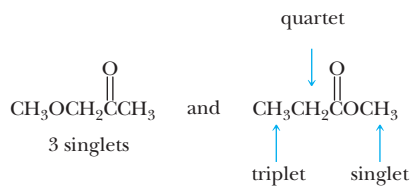


11.12 (a) Both compounds will have three signals.

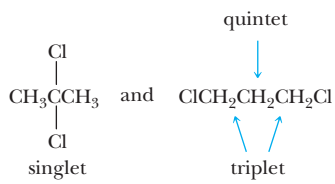
(b) 3 : 3 : 2

(c) The chemical shift of the CH_2 hydrogens in (1) will be more downfield than that of the CH_2 hydrogens in (2).

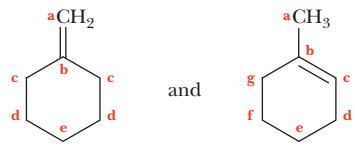
11.13 (a) Each compound will have three signals.



(b) The compound on the left has one signal; the compound on the right has two signals.

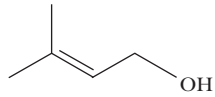


11.14 (a) The compound on the left has a plane of symmetry and will have five ^{13}C signals, while the compound on the right will have seven signals.

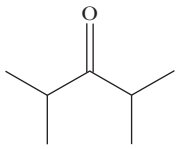


(b) The compound on the left will have six ^{13}C signals, while the compound on the right, which has symmetry, will have three signals.

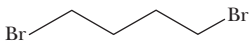
11.15



11.16



11.17



End-of-Chapter Problems

Electromagnetic Radiation

11.19 Microwave radiation with an energy of 5.9×10^{-5} kJ/mol (1.4×10^{-5} kcal/mol)

Interpreting Infrared Spectra

11.21 (a) 6

(b) 3

(c) 4

(d) 1

(e) 5

(f) 1

11.23 (a) 1

(b) 1 π bond

(c) Carbon–carbon double bond that is not bonded to any hydrogen atoms

11.25 (a) 0

(b) 0

(c) Primary amine

11.27 (a) 1

(b) 1 ring or π bond

(c) An ester alone or an aldehyde/ketone in conjunction with an ether

11.29 (a) 1-Butanol will have a strong, broad O—H absorption between 3200 and 3400 cm^{-1}.

(b) Butanoic acid will have a strong C=O absorption near 1700 cm^{-1}.

(c) Butanoic acid will have a broad O—H absorption between 2400 and 3400 cm^{-1}.

(d) Butanal will have a strong C=O absorption near 1700 and 1725 cm^{-1}. 1-Butene will have a vinylic =C—H absorption near 3100 cm^{-1}.

(e) Butanone will have a strong C=O absorption near 1725 cm^{-1}. 2-Butanol will have a strong, broad O—H absorption between 3200 and 3400 cm^{-1}.

(f) 2-Butene will have a vinylic =C—H absorption near 3100 cm^{-1}.

11.31 (a) 3200 cm^{-1}

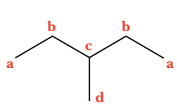
(b) 3050 cm^{-1}

(c) 1680 cm^{-1}

(d) Between 1450 and 1620 cm^{-1}

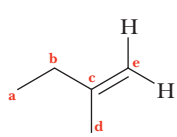
Equivalency of Hydrogens and Carbons

11.33 (a)



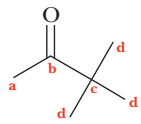
four signals

(b)



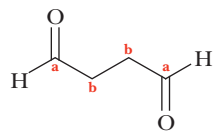
five signals

(c)



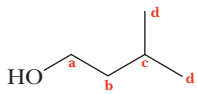
four signals

(d)



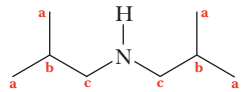
two signals

(e)



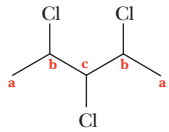
four signals

(f)



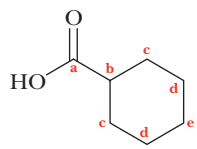
three signals

(g)



three signals

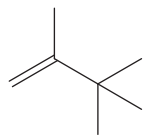
(h)



five signals

Interpreting ^{1}H-NMR and ^{13}C-NMR Spectra

11.35



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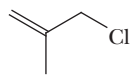
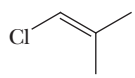
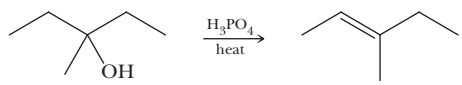


compound L



compound M

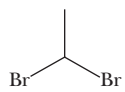
11.39



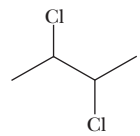
compound N

compound O

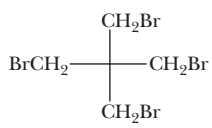
11.41 (a)



(b)



(c)



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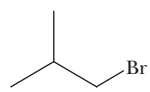

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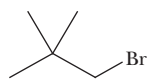

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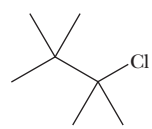

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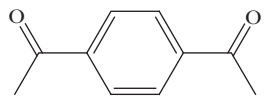

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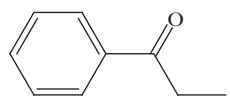

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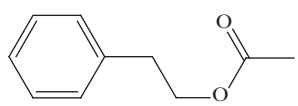
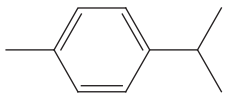
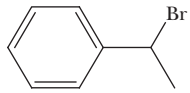
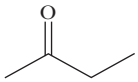
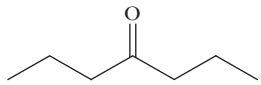
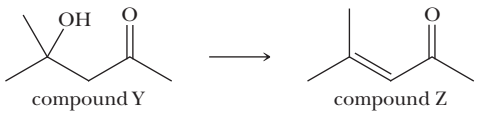


(c) 

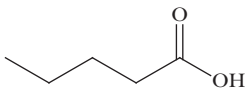
(d) 

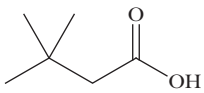
11.47 (a) 

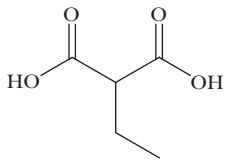
(b) 

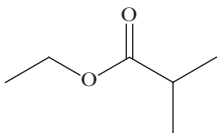
11.49 

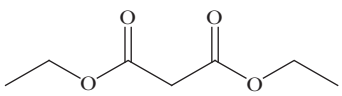
compound Y compound Z

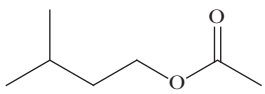
11.51 (a) 

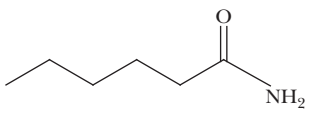
(b) 

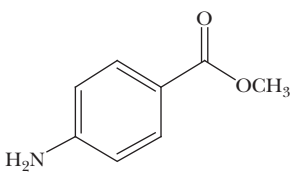
(c) 

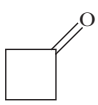
11.53 (a) 

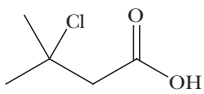
(b) 

(c) 

11.55 

11.57 

11.59 

11.61 

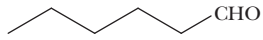
Looking Ahead

11.63 The C═O stretching absorption for acetate will be at a lower wavenumber.

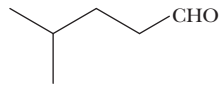
CHAPTER 12 Aldehydes and Ketones

Problems

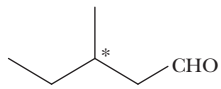
12.1 (a) 2,2-Dimethylpropanal
(b) (*R*)-3-Hydroxycyclohexanone
(c) (*R*)-2-Phenylpropanal
(d) (*Z*)-2-Ethyl-2-heptenal

12.2 

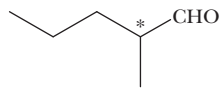
Hexanal



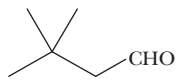
4-Methylpentanal



3-Methylpentanal

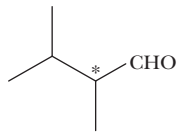


2-Methylpentanal

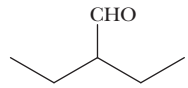


3,3-Dimethylbutanal

2,2-Dimethylbutanal



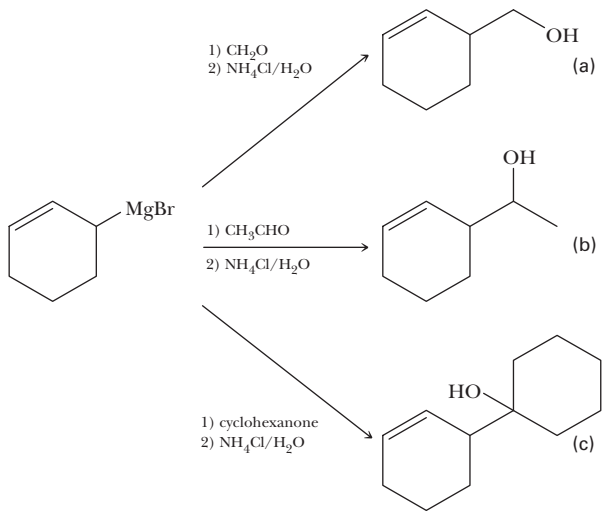
2,3-Dimethylbutanal

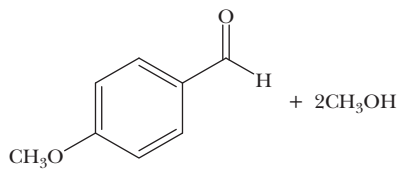


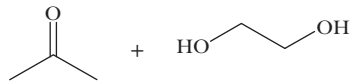
2-Ethylbutanal

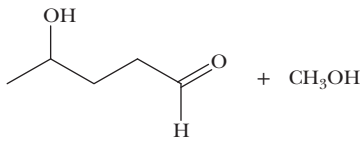
12.3 (a) 2-Hydroxypropanoic acid
(b) 2-Oxopropanoic acid
(c) 4-Aminobutanoic acid

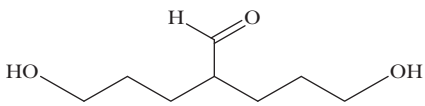
12.4 Grignard reagents are highly basic and are destroyed by acids. Both of these reagents contain ionizable hydrogens.

12.5 

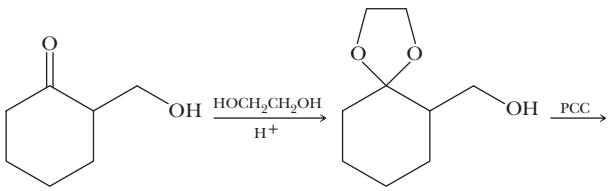
12.6 (a) 

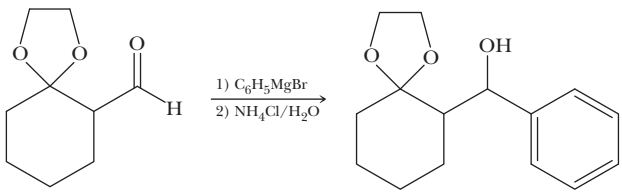
(b) 

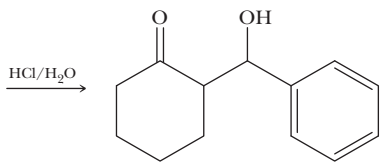
(c) 

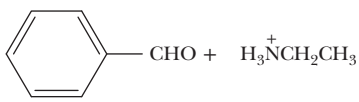
(d) 

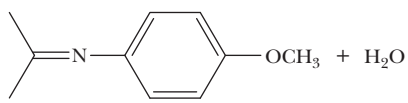
12.7

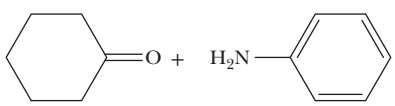


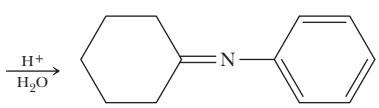


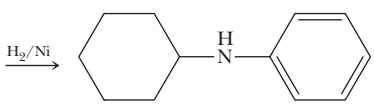


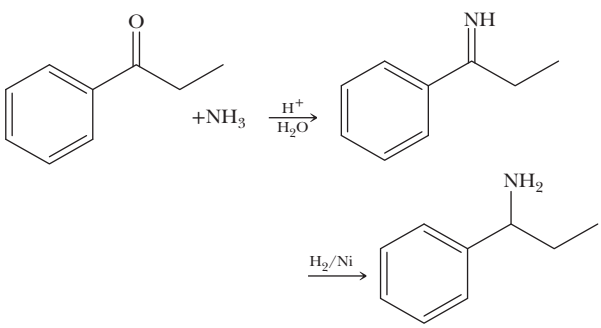
12.8 (a) 

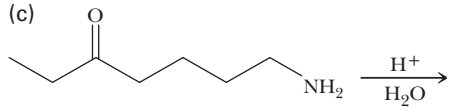
(b) 

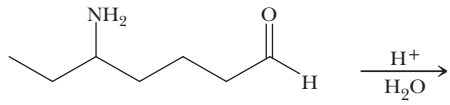
12.9 (a) 

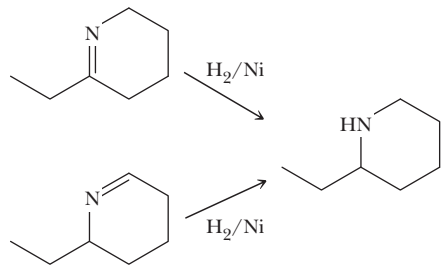


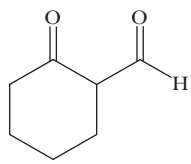


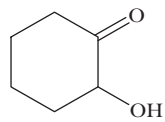
(b) 

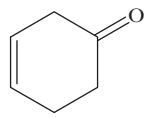
(c) 

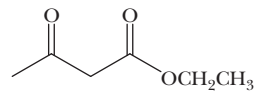


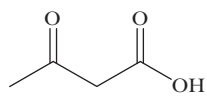


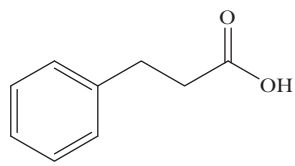
12.10 (a) 

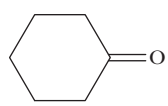
(b) 

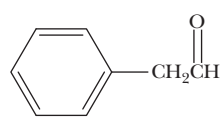
(c) 

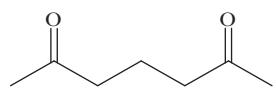
(d) 

12.11 (a) 

(b) 

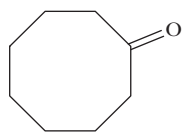
12.12 (a) 

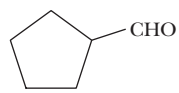
(b) 

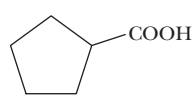
(c) 

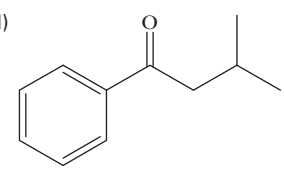
End-of-Chapter Problems

Preparation of Aldehydes and Ketones

12.13 (a) 

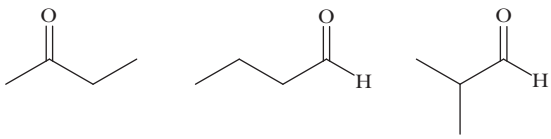
(b) 

(c) 

(d) 

Structure and Nomenclature

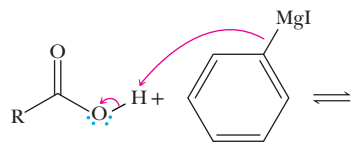
12.15



12.17 (a) 4-Heptanone
(b) (*S*)-2-Methylcyclopentanone
(c) (*Z*)-2-Methyl-2-pentenal
(d) (*S*)-2-Hydroxypropanal
(e) 2-Methoxyacetophenone
(f) 2,2-Dimethyl-3-oxopropanoic acid
(g) (*S*)-2-Propylcyclopentanone
(h) 3,3-Dimethyl-5-oxooctanal

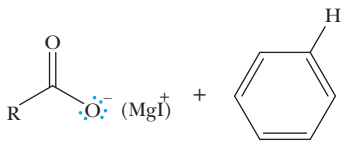
Addition of Carbon Nucleophiles

12.19



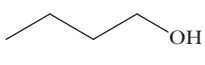
pK_a=5

stronger acid stronger base

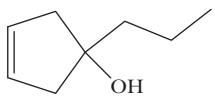


weaker base weaker acid

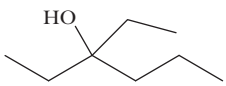
12.21 (a)



(b)

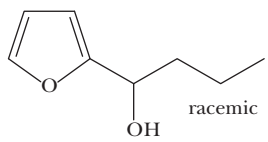


(c)



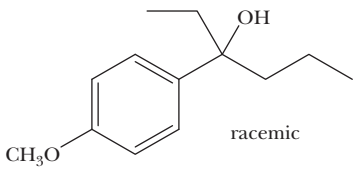
racemic

(d)



racemic

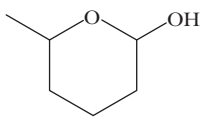
(e)



racemic

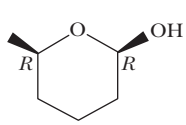
Addition of Oxygen Nucleophiles

12.23 (a)

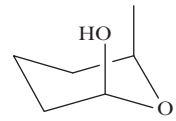


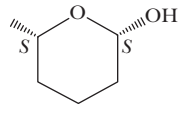
(b) 2 (c) 4

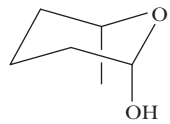
(d) and (e)

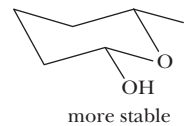


more stable

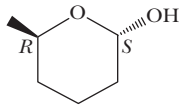


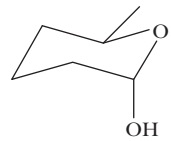


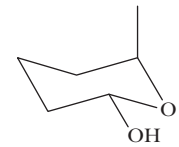




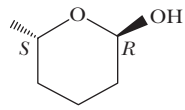
more stable

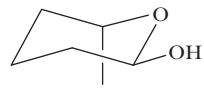


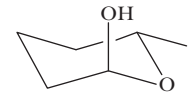




Both are approximately the same stability.

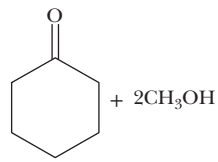




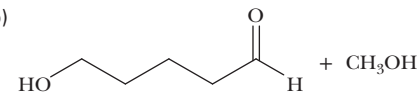


Both are approximately the same stability.

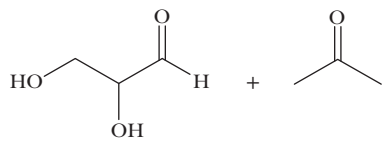
12.25 (a)



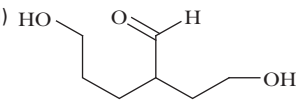
(b)



(c)

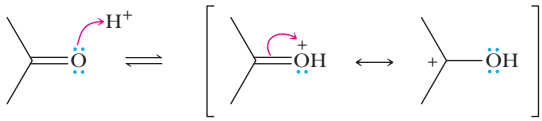


(d)



12.27

Step 1:



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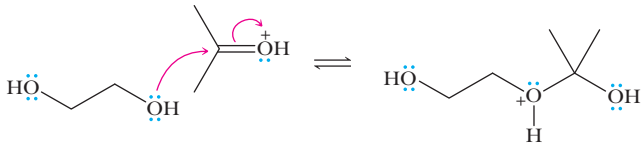

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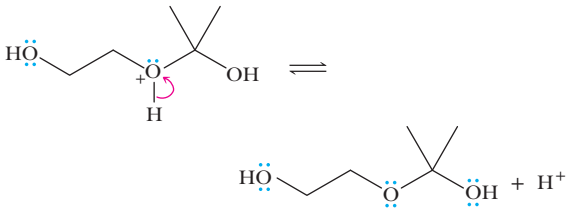

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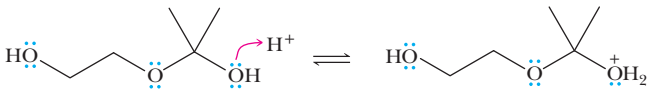

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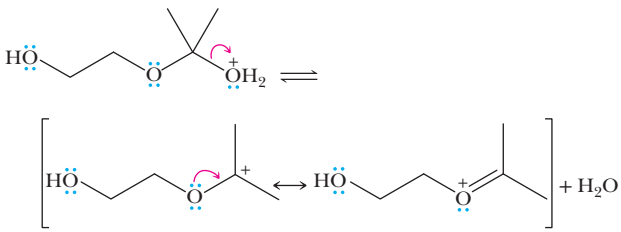

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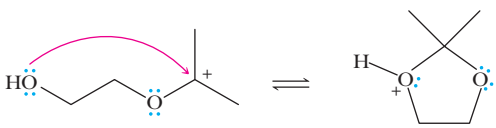

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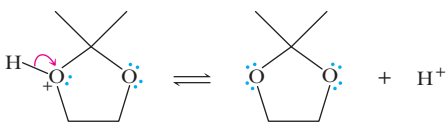
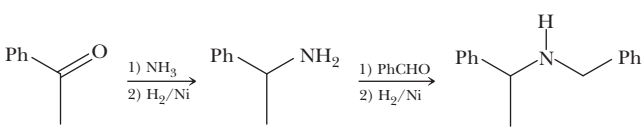
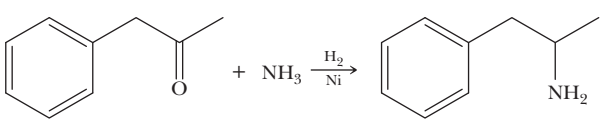


Addition of Nitrogen Nucleophiles

12.29

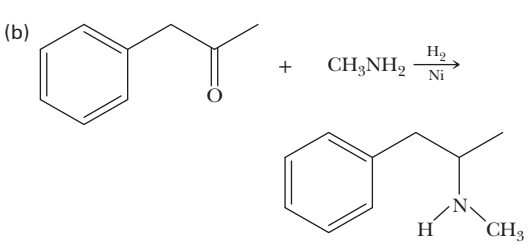


12.31 (a)



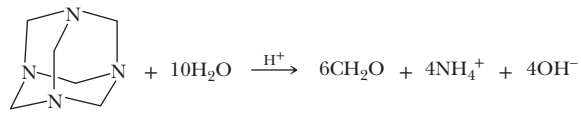
Amphetamine

(b)



Methamphetamine

12.33 (a)



(b) When methenamine is hydrolyzed, ammonium hydroxide is formed. Ammonium hydroxide is a base, so the pH will increase.

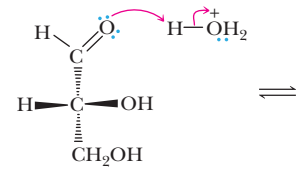
(c) Acetals are 1,1-diethers, where a single carbon atom is bonded to two—OR groups. In the case of methenamine, each carbon atom is bonded to two amine functional groups.

(d) The pH of blood plasma is slightly basic (pH of 7.4), but the pH of the urinary tract is acidic. Acetals (and methenamine, which is a nitrogen analog of an acetal) require acidic conditions for hydrolysis to occur, but they are stable under basic conditions.

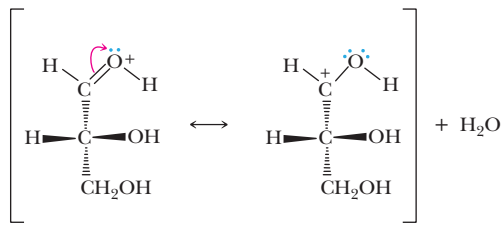
Keto–Enol Tautomerism

12.35

Step 1:



(*R*)-Glyceraldehyde



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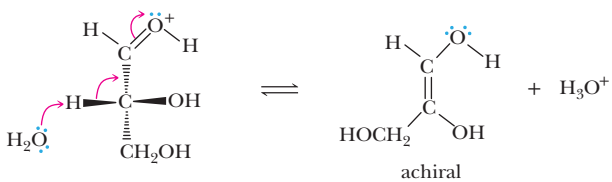
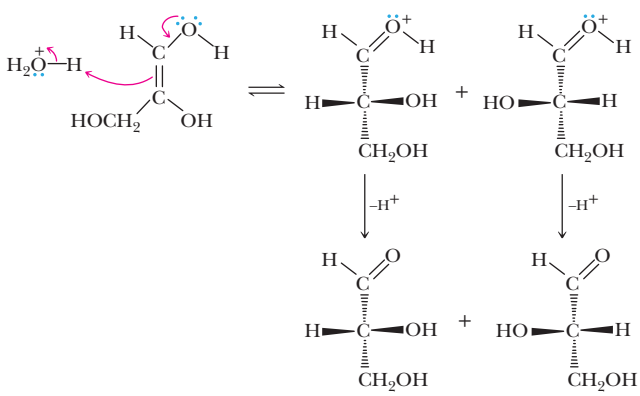


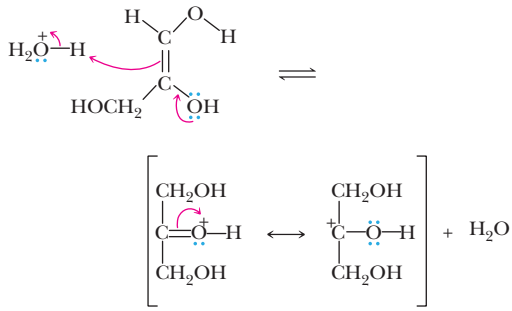
achiral

Step 3:

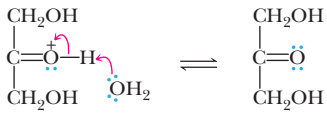


(*R*)-Glyceraldehyde (*S*)-Glyceraldehyde

Step 4:



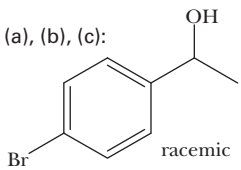
Step 5:



Oxidation/Reduction of Aldehydes and Ketones

12.37

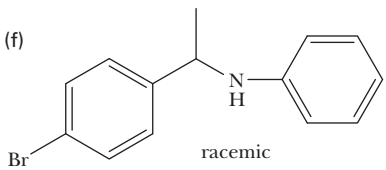
(a), (b), (c):



racemic

(d), (e): no reaction

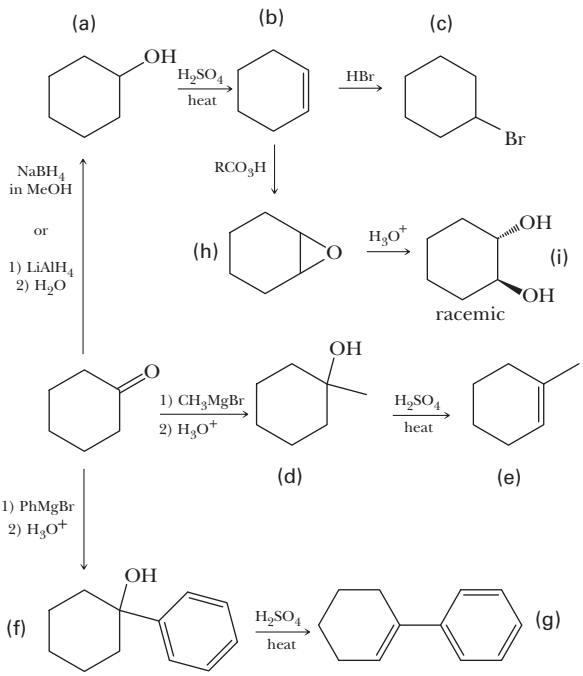
(f)



racemic

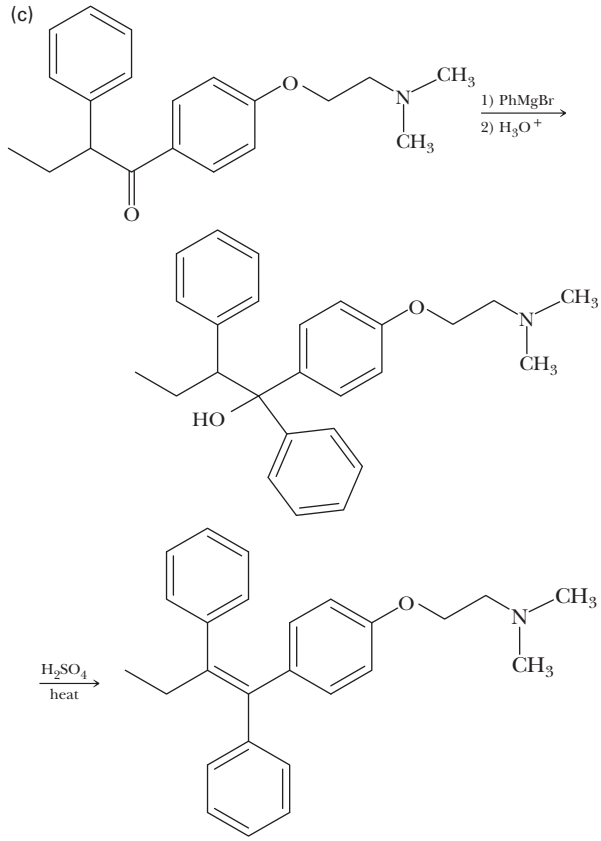
Synthesis

12.39



12.41 (a) 2 (b) *Z*

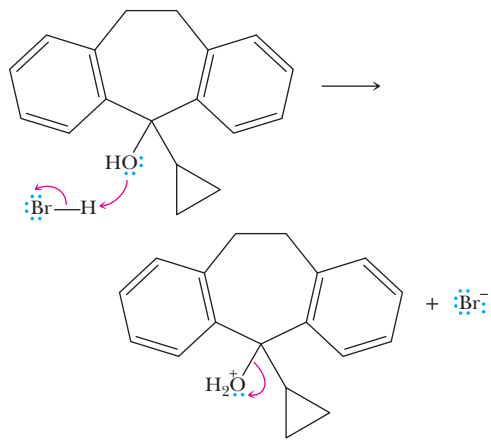
(c)



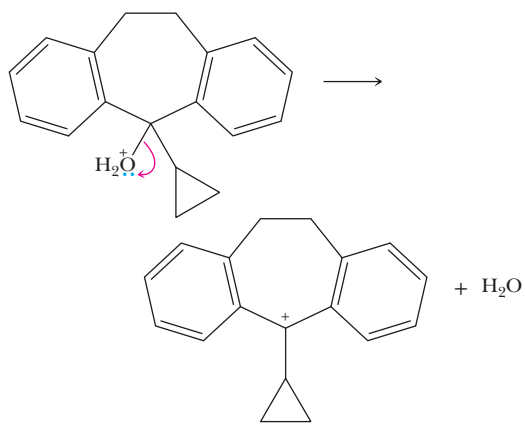
12.43 (a) Cyclopropylmagnesium bromide followed by acid treatment

(b)

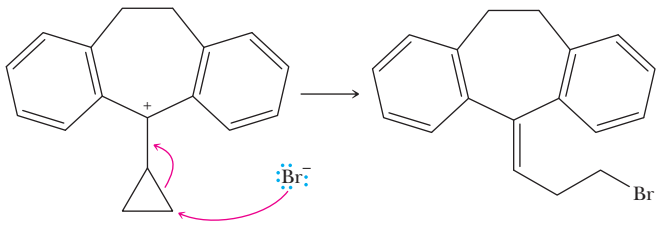
Step 1:



Step 2:



Step 3:



(c) 2 equivalents of dimethylamine

12.45 (a) Step 1 is a Friedel-Crafts acylation and involves the use of acetyl chloride (CH_3COCl) and a Lewis acid catalyst, such as $AlCl_3$.

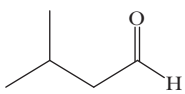
(b) Step 2: Cl_2 in acetic acid
Step 3: 2 equivalents of dimethylamine

(c) Step 4: $NaBH_4$ in an alcohol, or $LiAlH_4$ followed by water
Step 5: SOCl2 in pyridine

(d) Step 6 is a Grignard reaction. The starting material is first treated with magnesium in ether to prepare the Grignard reagent, which is subsequently treated with cyclohexanone followed by acid.

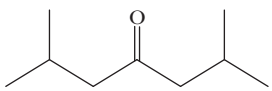
Spectroscopy

12.47



3-Methylbutanal

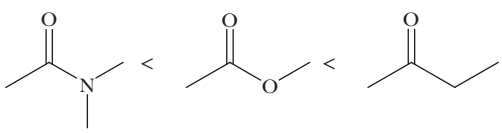
12.49



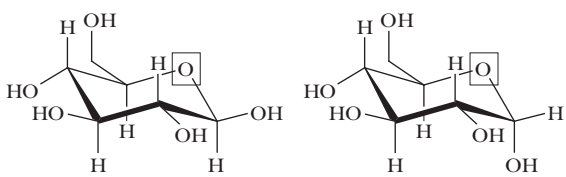
2,6-Dimethyl-4-heptanone

Looking Ahead

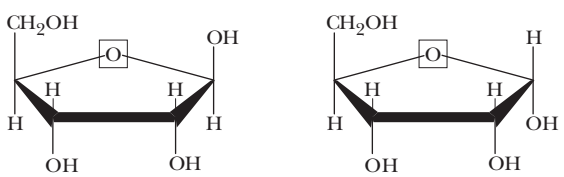
12.51



12.53 (a)



(b)



CHAPTER 13 Carboxylic Acids

Problems

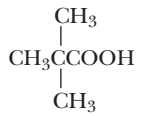
13.1

(a) (*R*)-2,3-Dihydroxypropanoic acid (b) (*Z*)-Butenedioic acid

(c) (*R*)-3,5-Dihydroxy-3-methylpentanoic acid

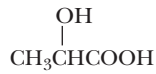
(d) (*S*)-2-Hydroxypropanoic acid

13.2



2,2-Dimethylpropanoic acid
pK_a 5.03

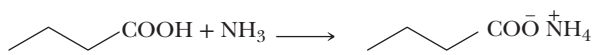
Trifluoroacetic acid
pK_a 0.22



2-Hydroxypropanoic acid
(Lactic acid)
pK_a 3.85

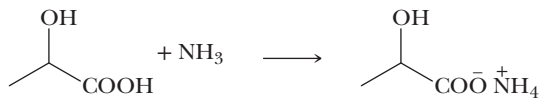
13.3

(a)



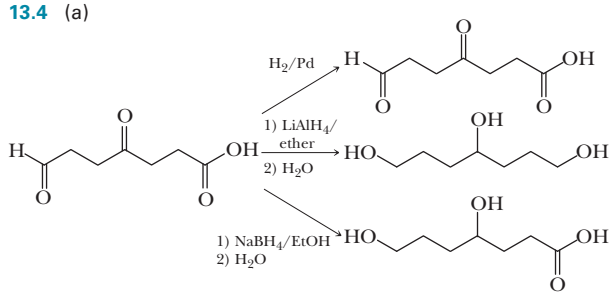
Butanoic acid — Ammonium butanoate

(b)

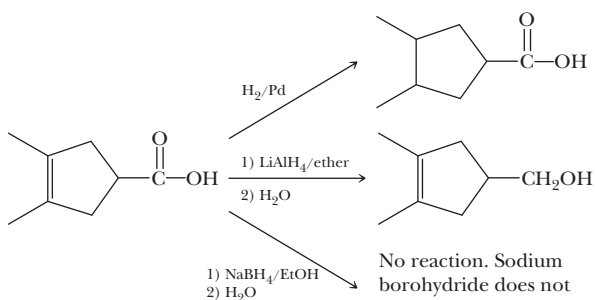


2-Hydroxypropanoic acid (Lactic acid) — Ammonium 2-hydroxypropanoate (Ammonium lactate)

13.4 (a)



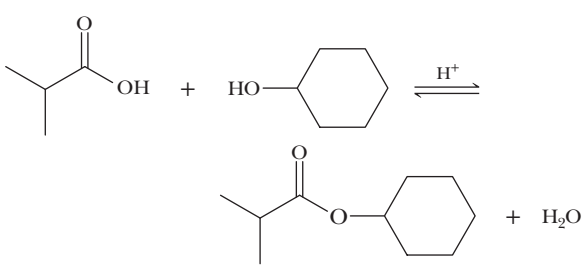
(b)



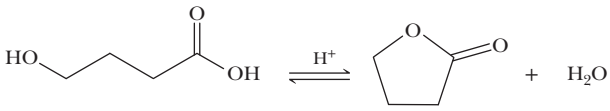
No reaction. Sodium borohydride does not reduce alkenes or acids.

13.5

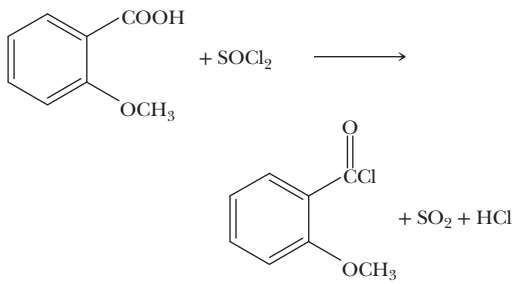
(a)



(b)



13.6 (a)



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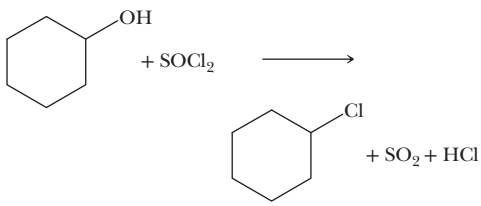
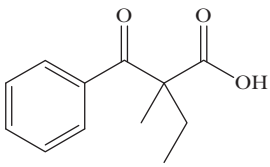


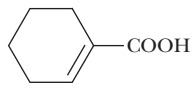
13.7



β-Ketoacid

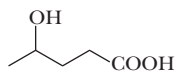
End-of-Chapter Problems

13.9 (a)



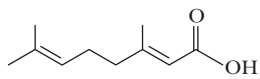
1-Cyclohexenecarboxylic acid

(b)



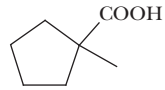
4-Hydroxypentanoic acid

(c)



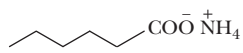
(*E*)-3,7-Dimethyl-2,6-octadienoic acid

(d)



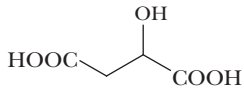
1-Methylcyclopentanecarboxylic acid

(e)



Ammonium hexanoate

(f)

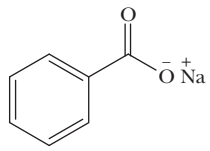


2-Hydroxybutanedioic acid

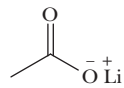
13.11 (a) 3,5-Tetradecadienoic acid

(b) 4

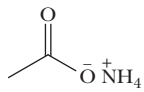
13.13 (a)



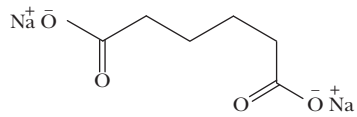
(b)



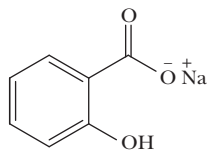
(c)



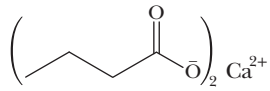
(d)



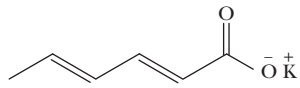
(e)



(f)



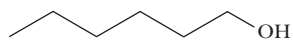
13.15



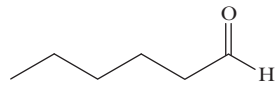
13.17 (a) $CH_3(CH_2)_6CHO < CH_3(CH_2)_6CH_2OH < CH_3(CH_2)_5COOH$

(b) $CH_3CH_2OCH_2CH_3 < CH_3CH_2CH_2CH_2OH < CH_3CH_2COOH$

13.19 (a)



(b)



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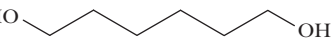
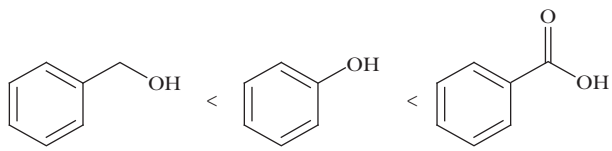
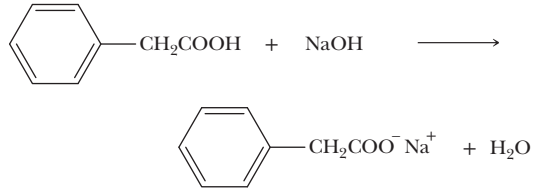


13.21



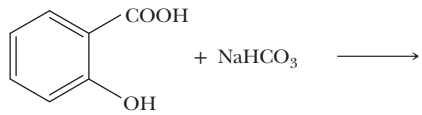
13.23 (a)

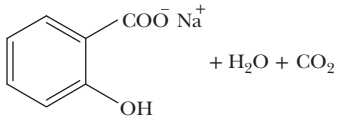


(b) $CH_3CH{=}CHCH_2COOH + NaHCO_3 \longrightarrow$

$CH_3CH{=}CHCH_2COO^-Na^+ + H_2O + CO_2$

(c)





(d) $CH_3CH(OH)COOH + H_2NCH_2CH_2OH \longrightarrow$

$CH_3CH(OH)COO^- \quad H_3\overset{+}{N}CH_2CH_2OH$

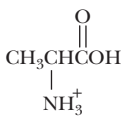
(e) $CH_3CH{=}CHCH_2COO^-Na^+ + HCl \longrightarrow$

$CH_3CH{=}CHCH_2COOH + NaCl$

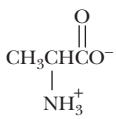
13.25 Salicylate anion

13.26 Lactic acid itself

13.29 (a)



(b)



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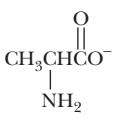
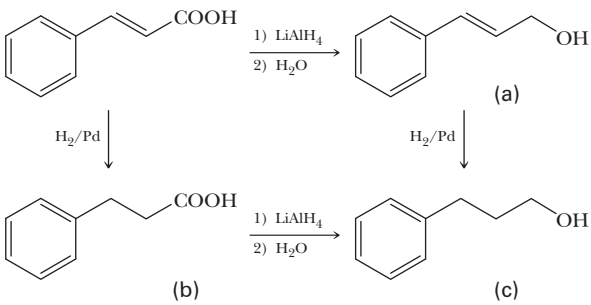
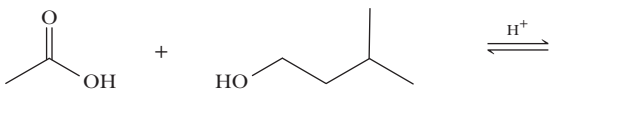
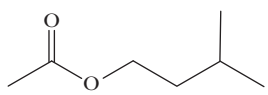


13.31



13.33 (a)





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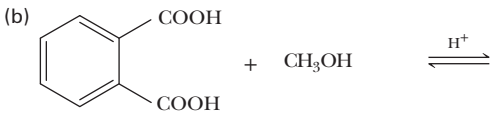

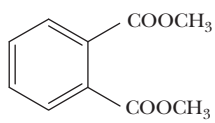

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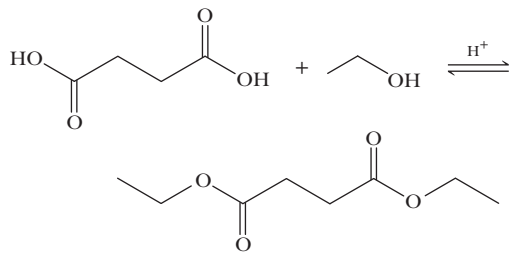

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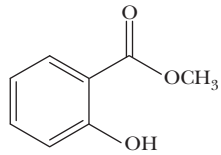
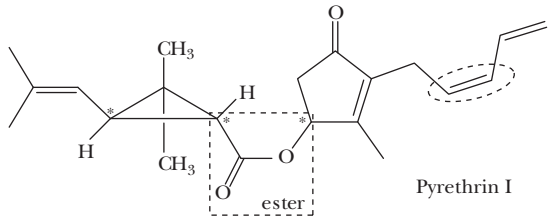
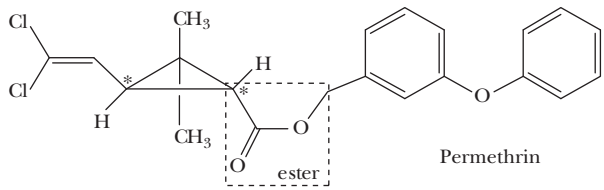


13.37 (a)



Pyrethrin I

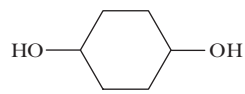


Permethrin

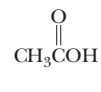
(b) Yes, 16

(c) Yes, 4

13.39 (a)

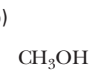


alcohol



carboxylic acid

(b)

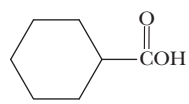


alcohol

carboxylic acid

(c)

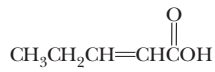
alcohol



carboxylic acid

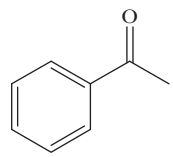
(d)

alcohol

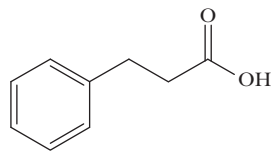


carboxylic acid

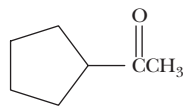
13.41 (a)



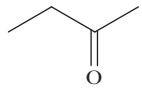
(b)



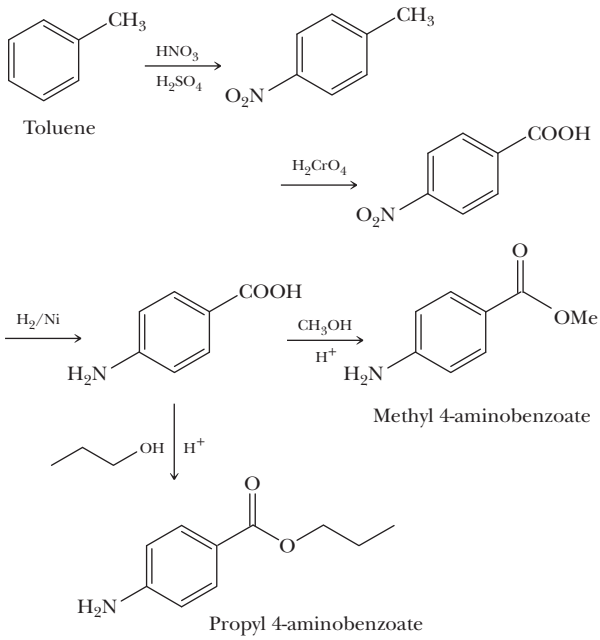
(c)



(d)



13.43

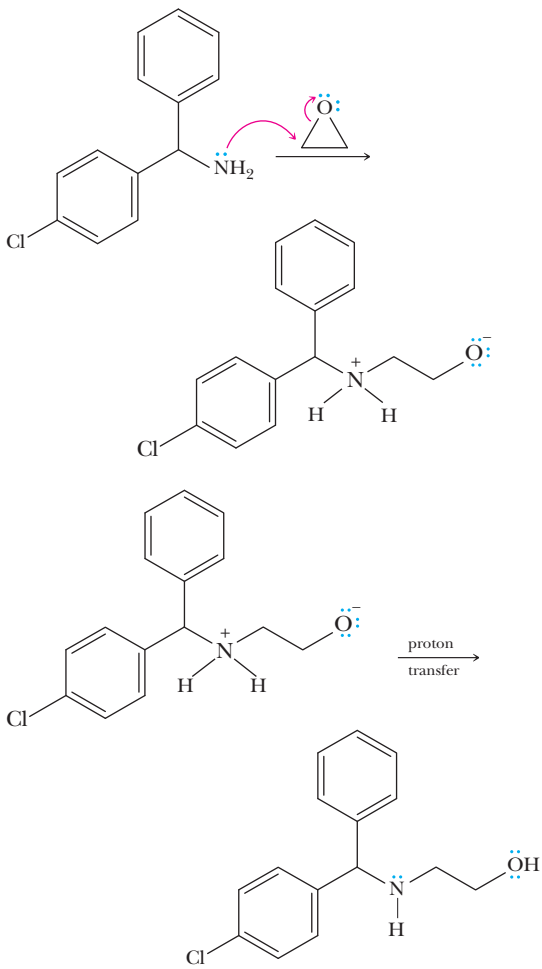


13.45 (a) $SOCl_2$ in the presence of a base, such as pyridine.

(b) Friedel–Crafts acylation with aluminum chloride.

(c) NH_3 followed by catalytic hydrogenation, such as H_2/Pt.

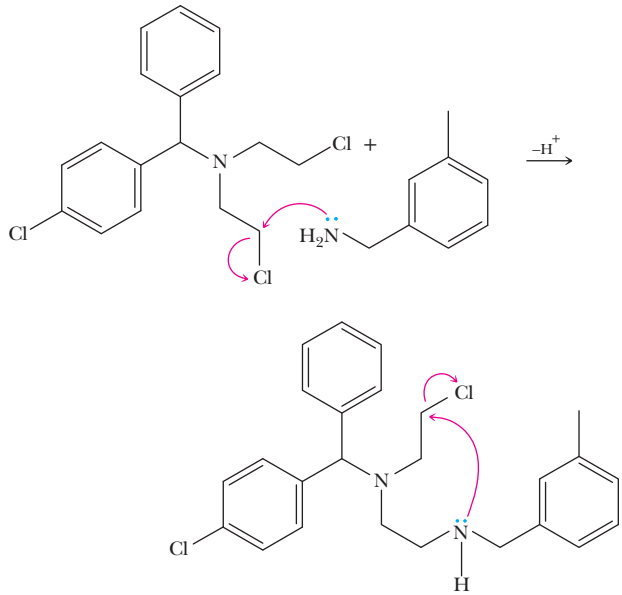
(d)

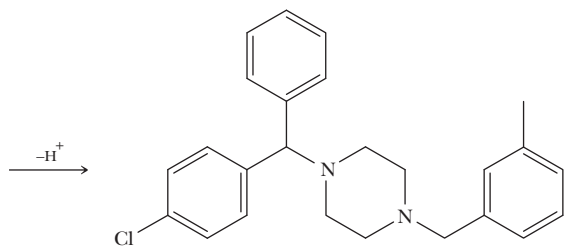


The mechanism repeats, using another equivalent of the epoxide.

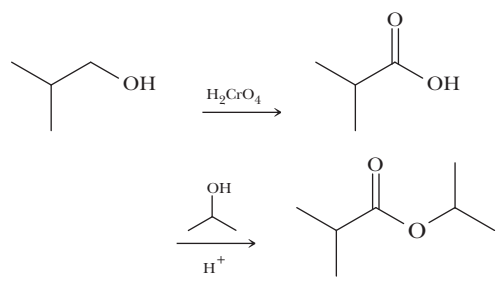
(e) $SOCl_2$ in the presence of a base, such as pyridine.

(f)





13.47 (a)



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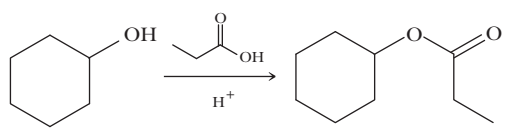

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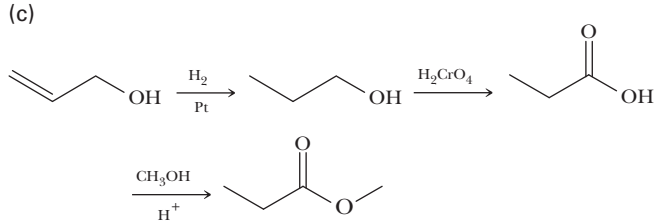

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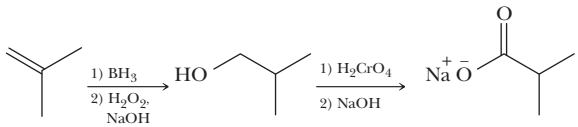

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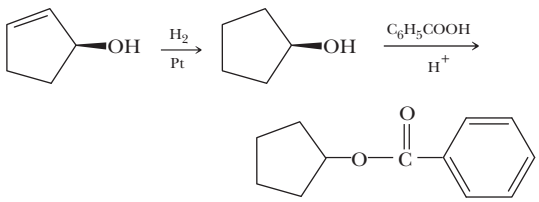

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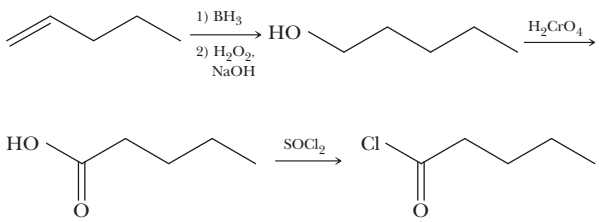

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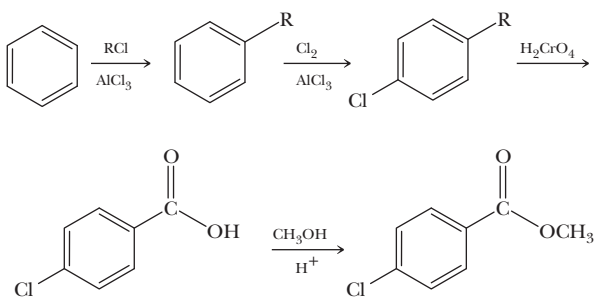

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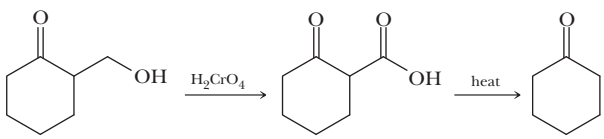

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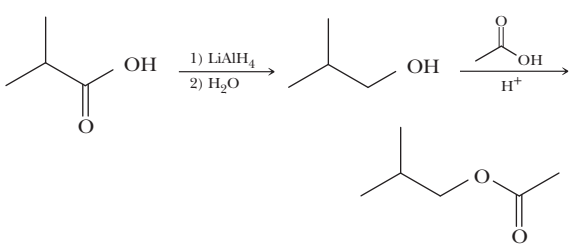

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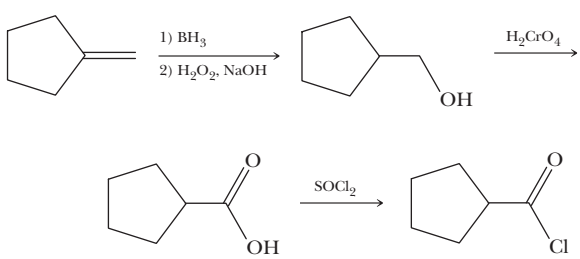

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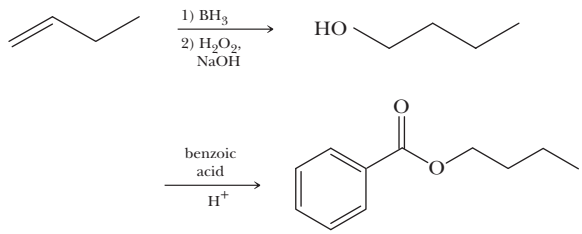

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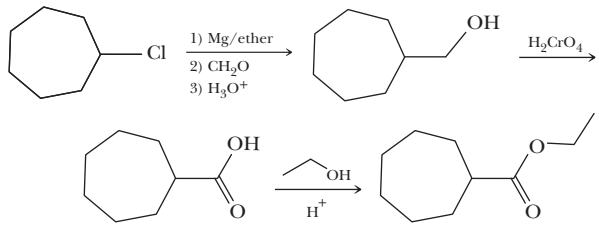

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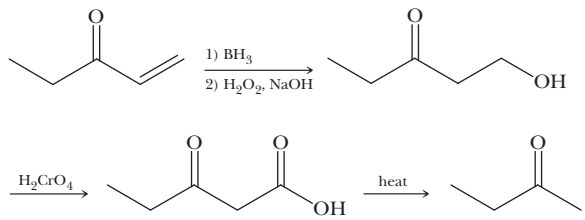

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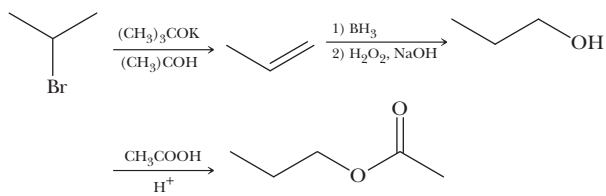

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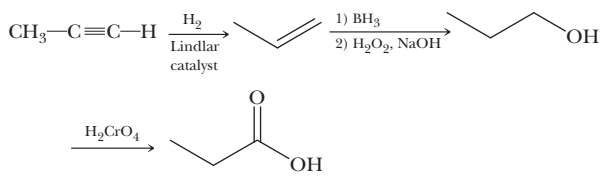

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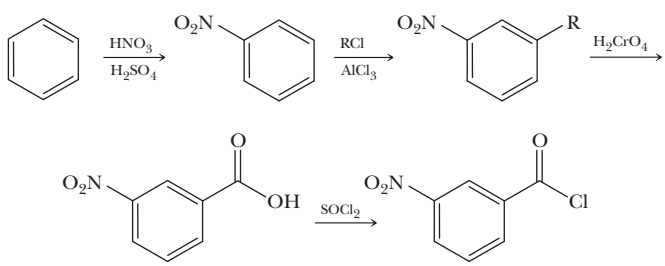
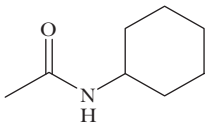


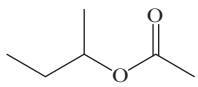
13.49 Carboxylate ion

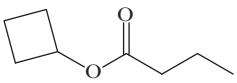
13.51 No, only with esters

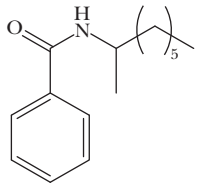
CHAPTER 14 Functional Derivatives of Carboxylic Acids

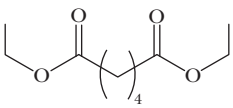
Problems

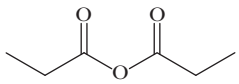
14.1 (a) 

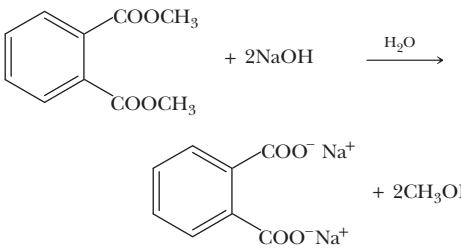
(b) 

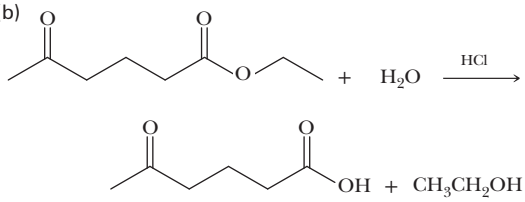
(c) 

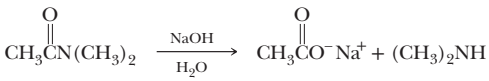
(d) 

(e) 

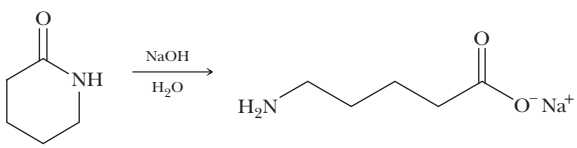
(f) 

14.2 (a) 

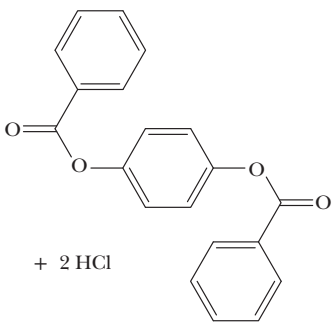
(b) 

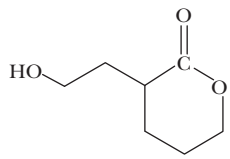
14.3 (a) 

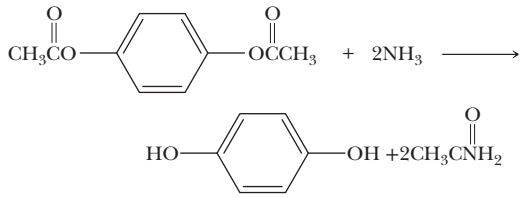
1 mole of NaOH needed for every mole of amide

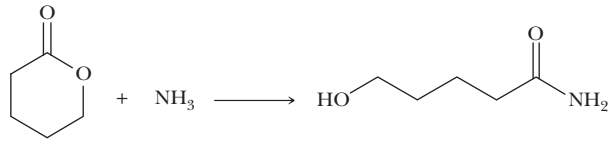
(b) 

1 mole of NaOH needed for every mole of amide

14.4 (a) 

(b) 

14.5 (a) 

(b) 

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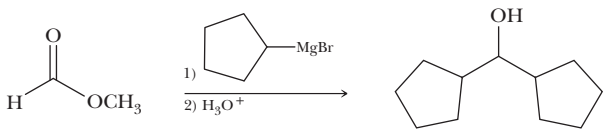
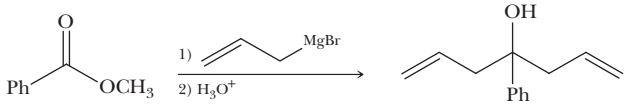
(a) 

(b) 

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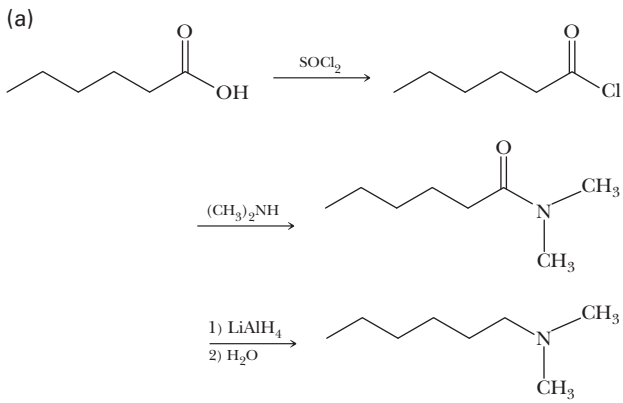
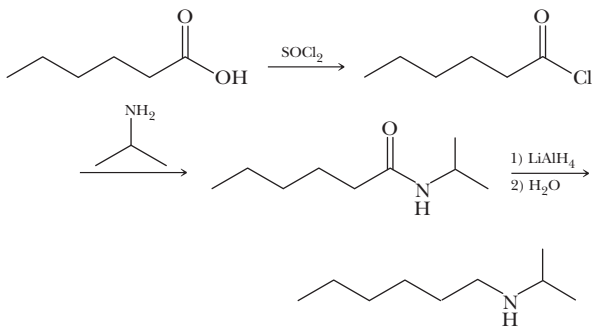
(a) 

(b) 

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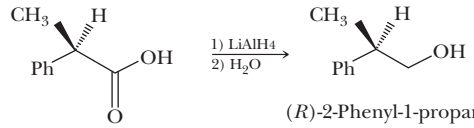
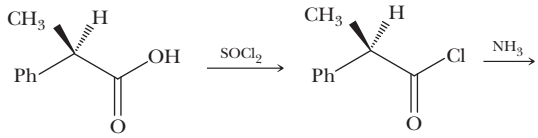
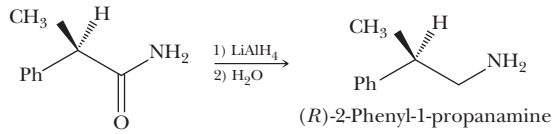


(*R*)-2-Phenyl-1-propanol

(b)



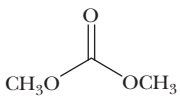


(*R*)-2-Phenyl-1-propanamine

End-of-Chapter Problems

14.9

(a)



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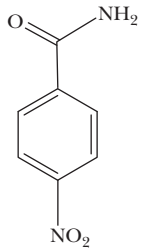

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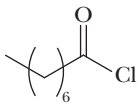

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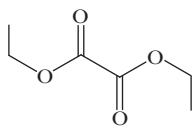

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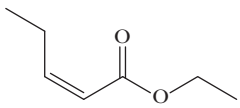

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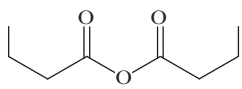

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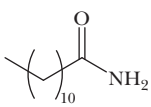

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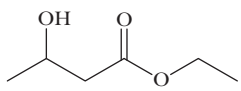

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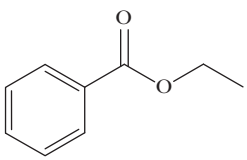

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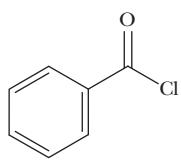

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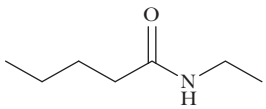

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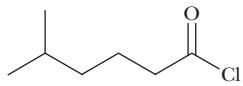
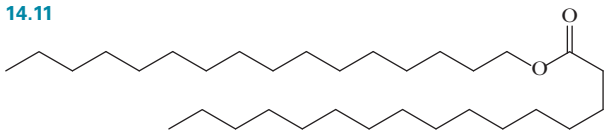


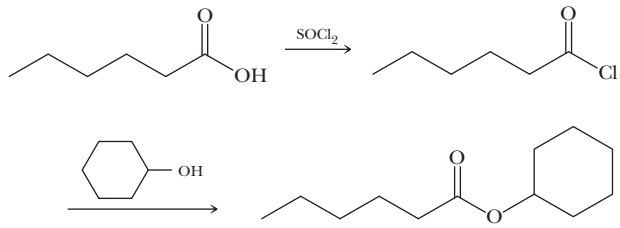
14.11



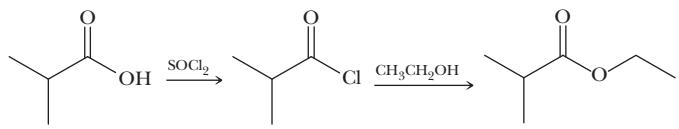
14.13 The strength of the hydrogen-bonding interactions in butanoic acid is greater than the increase in dispersion forces when going from butanoic acid to its propyl ester.

14.15 3 < 1 < 4 < 2

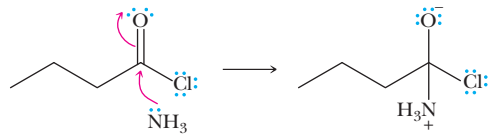
14.17 (a)



(b)



14.19 (a) Step 1:



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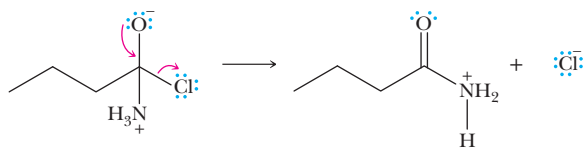
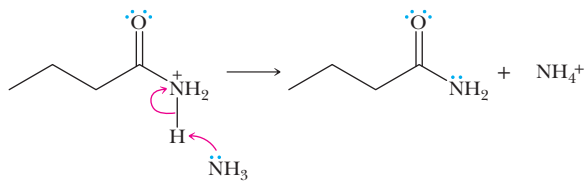
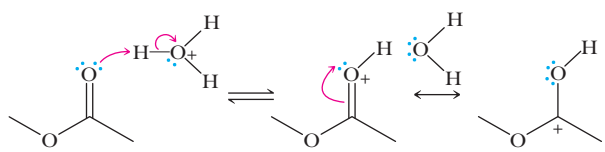


Step 3:



(b) Step 1:



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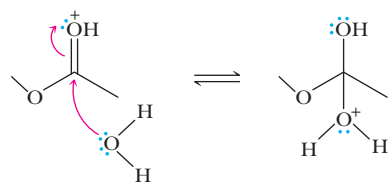

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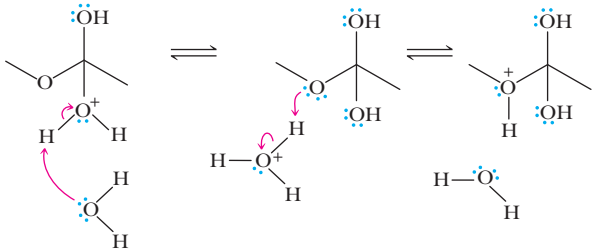

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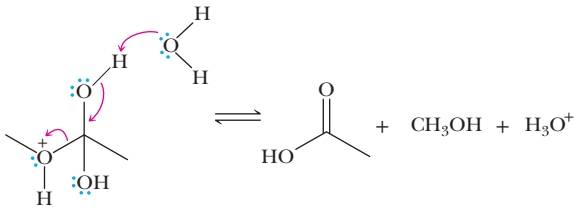

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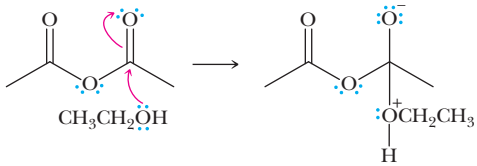

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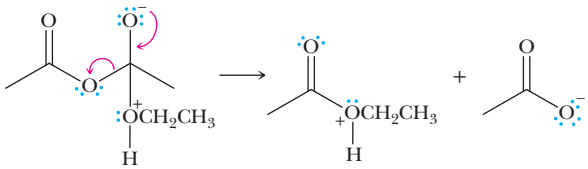
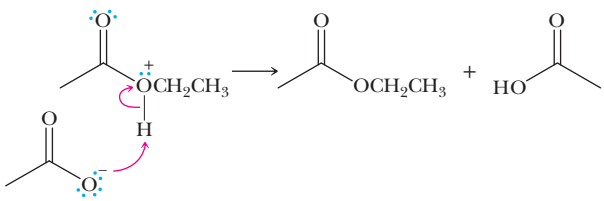
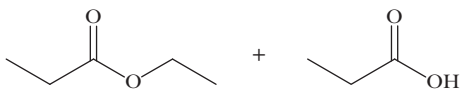


Step 3:



14.21 (a)



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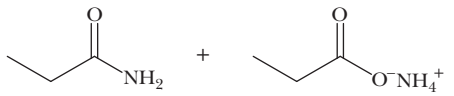
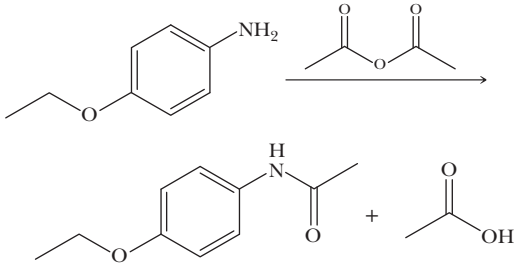
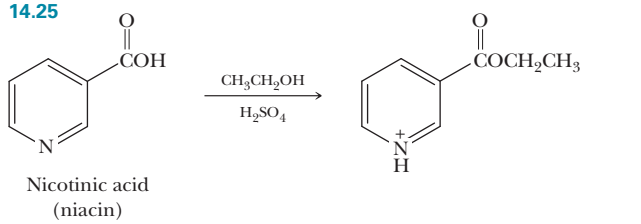


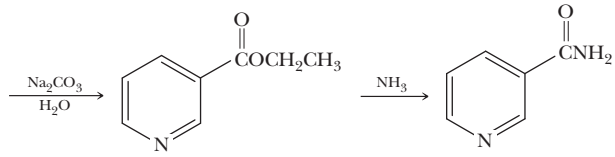
14.23



14.25

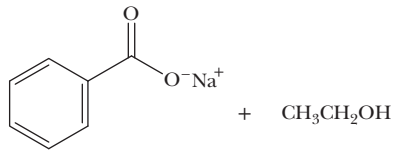


Nicotinic acid (niacin)



Ethyl nicotinate Nicotinamide

14.27 (a)



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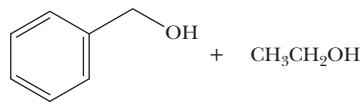

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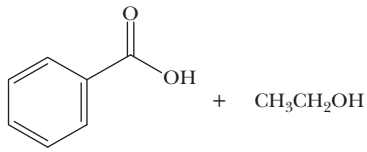
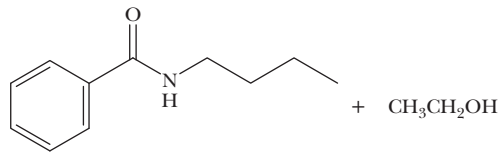
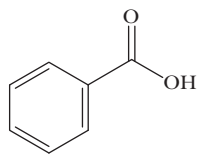


(d)

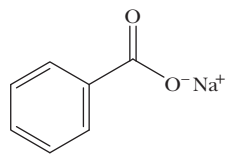


(e) $(C_6H_5)_3COH + CH_3CH_2OH$

14.29 (a)



(b)



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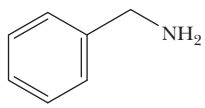
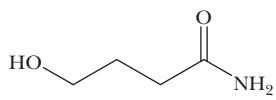


14.31 (a)



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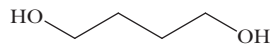

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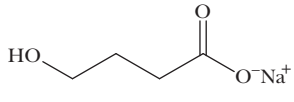
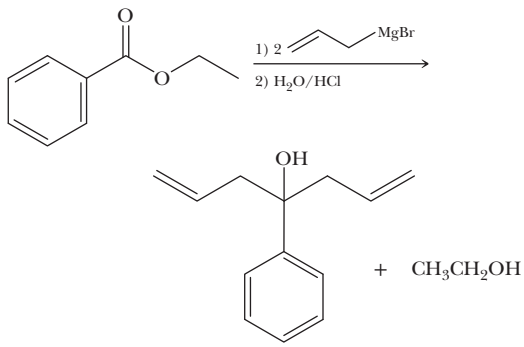


14.33 (a)



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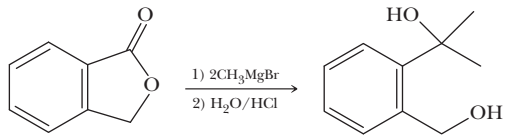

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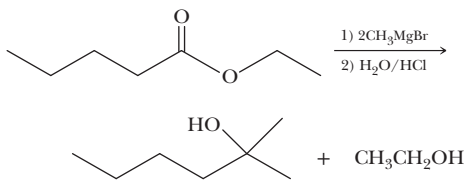
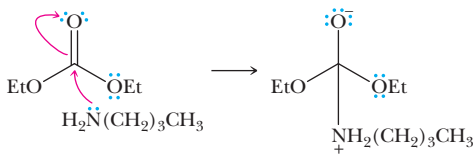


14.35 Step 1:



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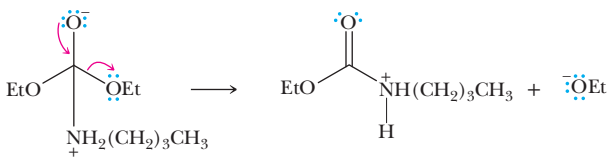
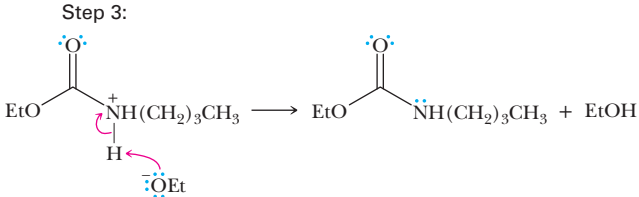
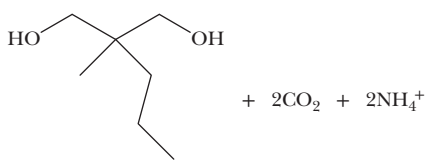


Step 3:

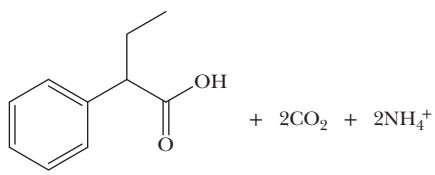


14.37 (a)



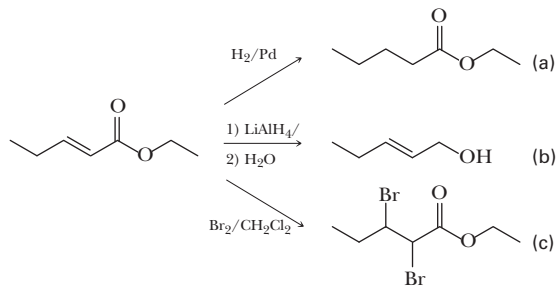
2-Methyl-2-propyl-1,3-propanediol

(b)

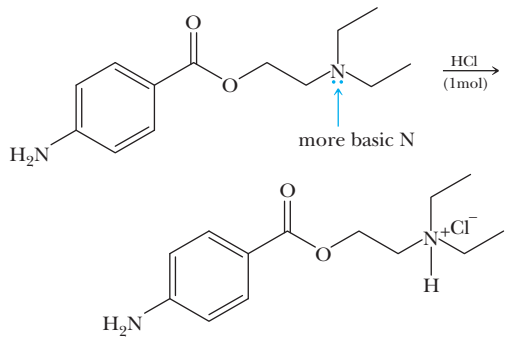


2-Phenylbutanoic acid

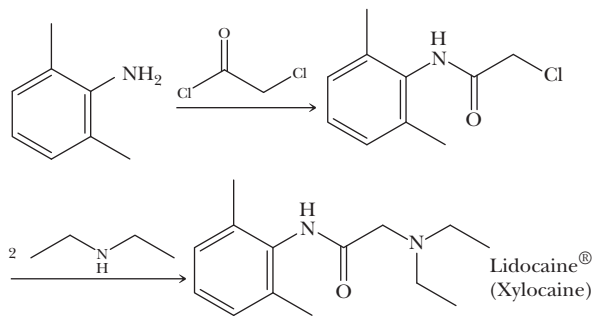
14.39



14.41



14.43 (a)



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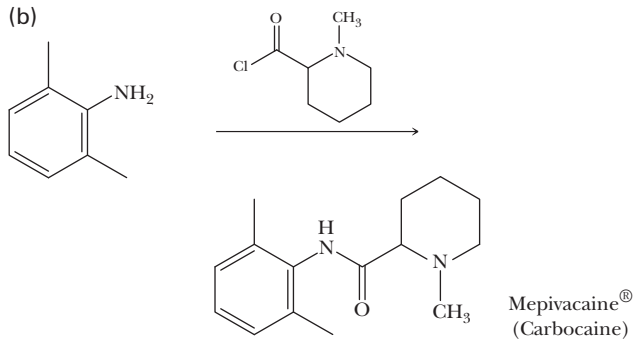

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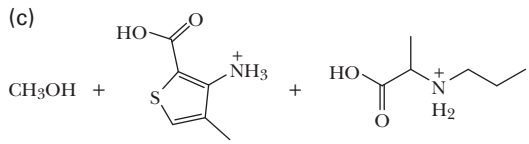
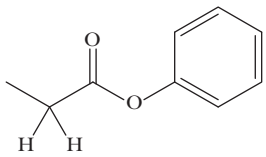


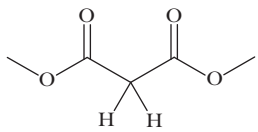
14.45 1) HNO_3/H_2SO_4 2) H_2CrO_4
3) CH_3OH/H_2SO_4 4) H_2/Ni

14.47 (a)



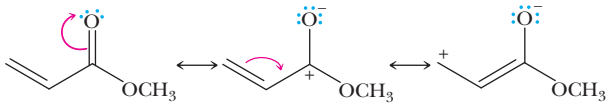
most acidic

(b)

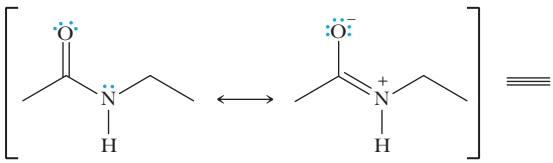


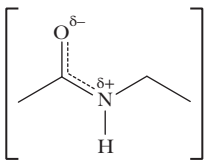
most acidic

14.49 Resonance structures can be drawn to show that the β-carbon is positively charged.



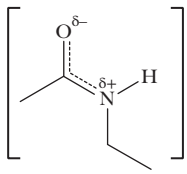
14.51 Amides have partial double-bond character between the carbon and nitrogen atoms.





resonance hybrid

high temperature

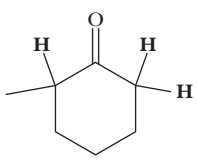


resonance hybrid

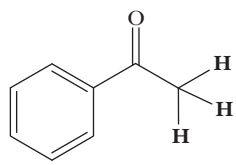
CHAPTER 15 Enolate Anions

Problems

15.1 (a)



(b)



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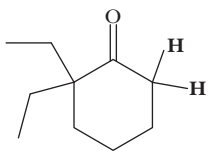
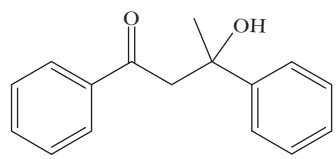


15.2 (a)



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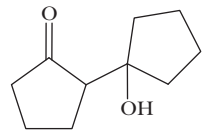

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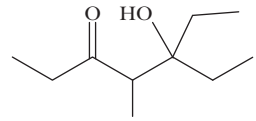

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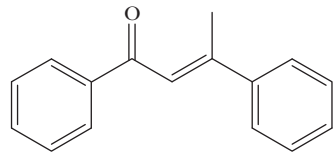

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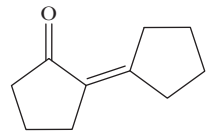

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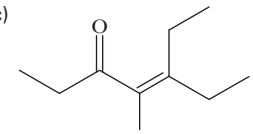

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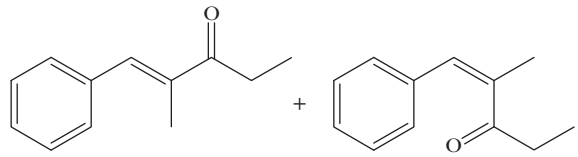

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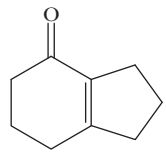

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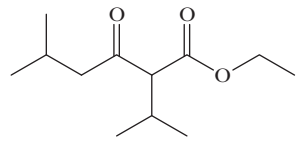

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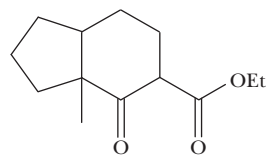

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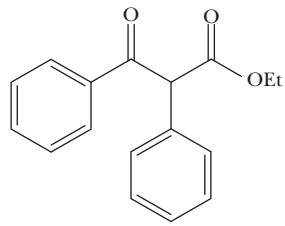

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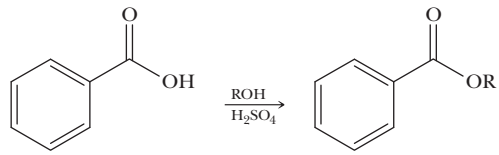
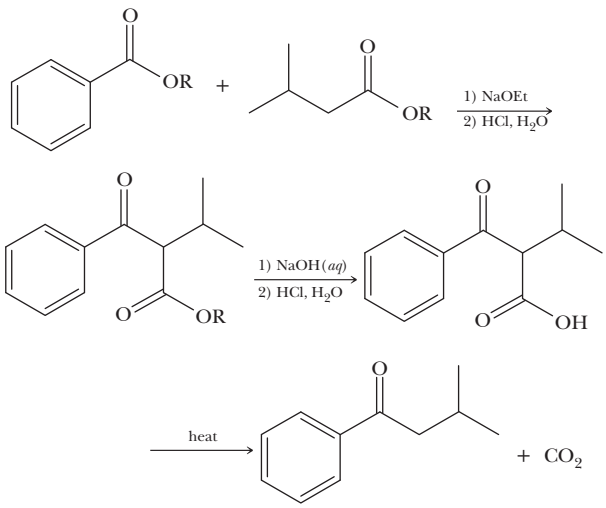
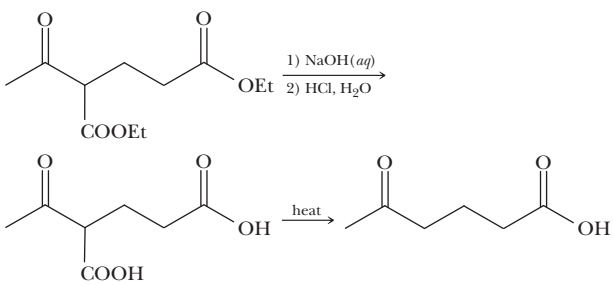




15.10 (a)



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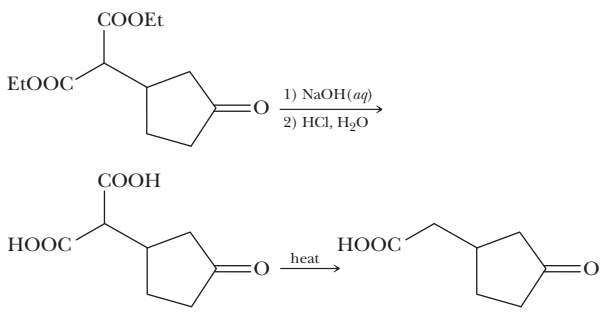

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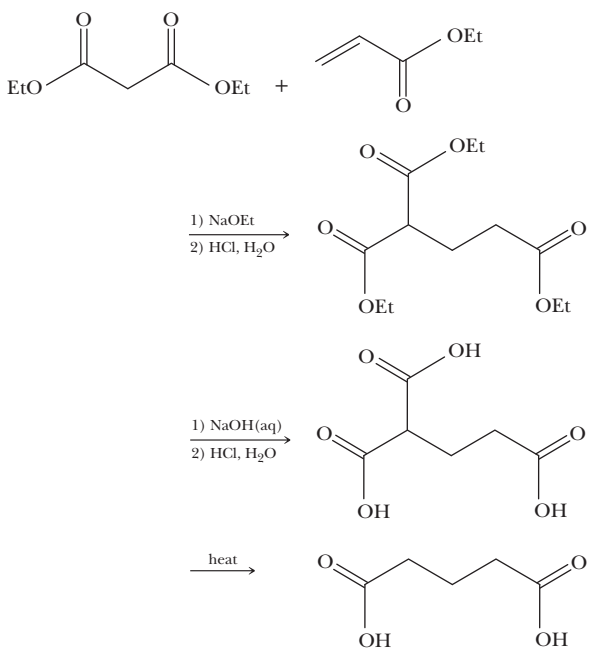

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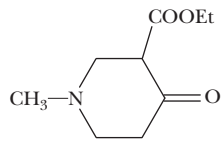
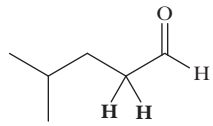


End-of-Chapter Problems

15.13 (a)



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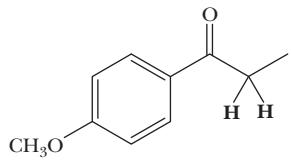

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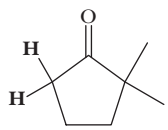

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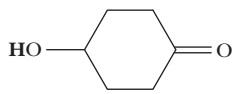

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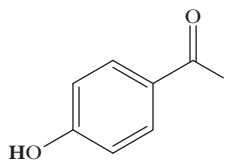

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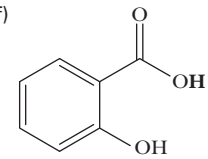

15.15

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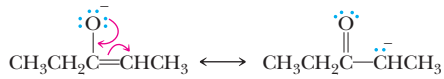

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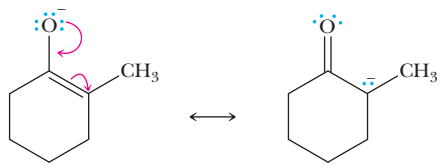

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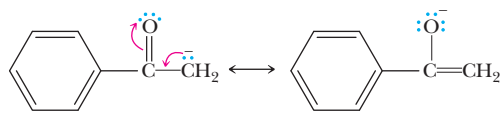

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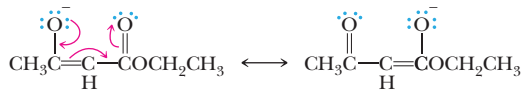

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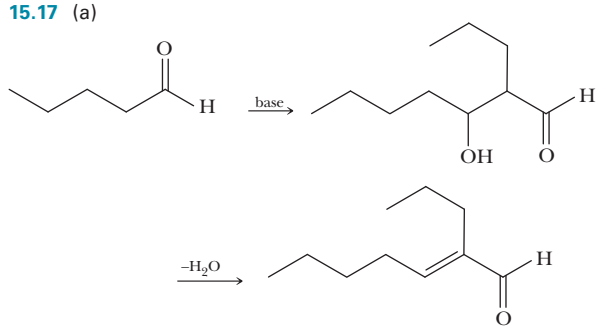

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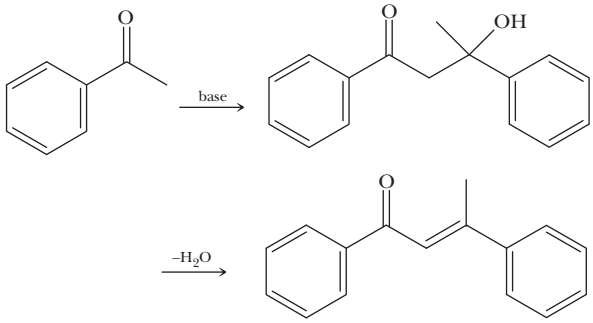

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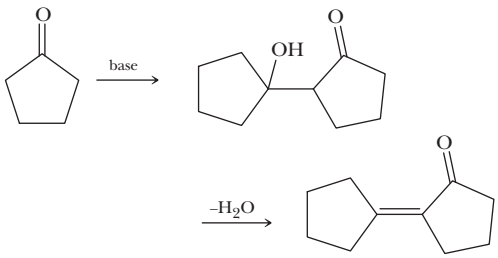

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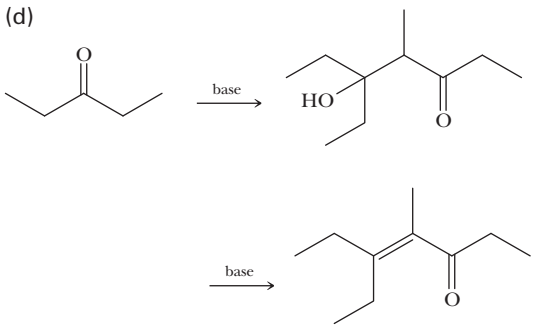

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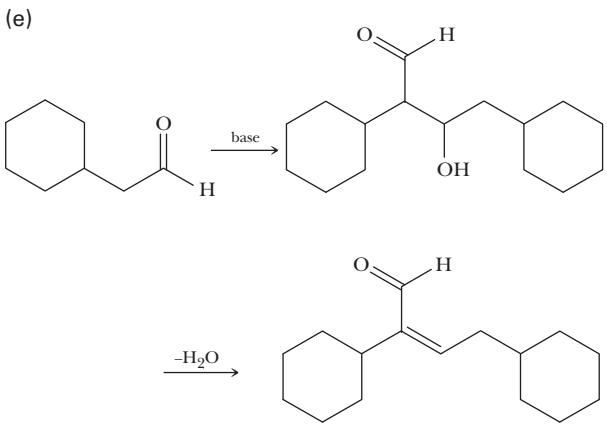

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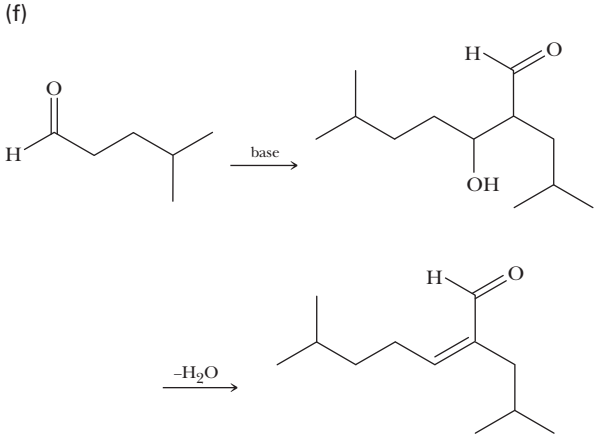
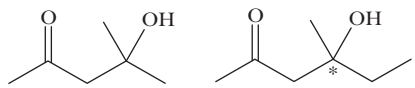


15.19 (a)



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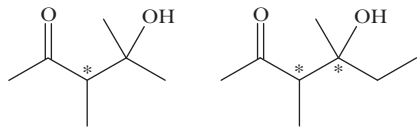

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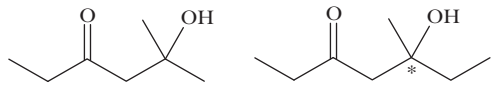
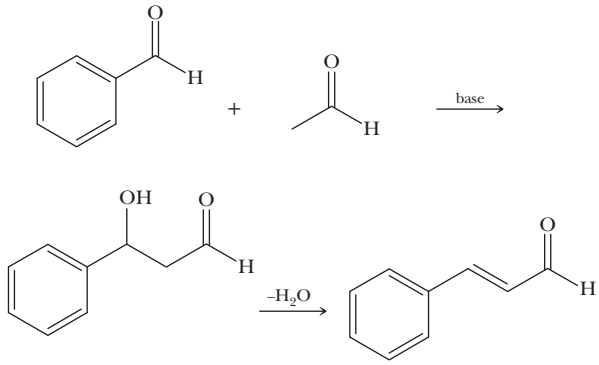


15.21 (a)



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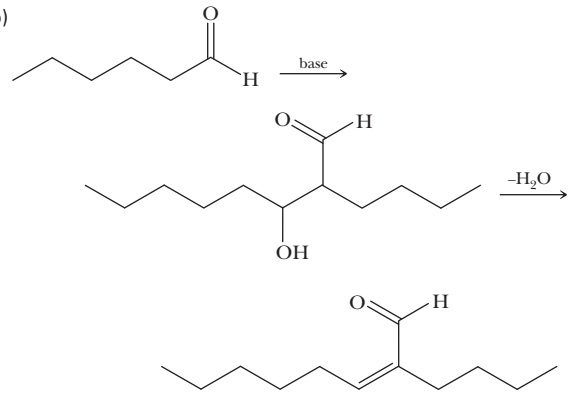

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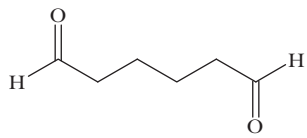
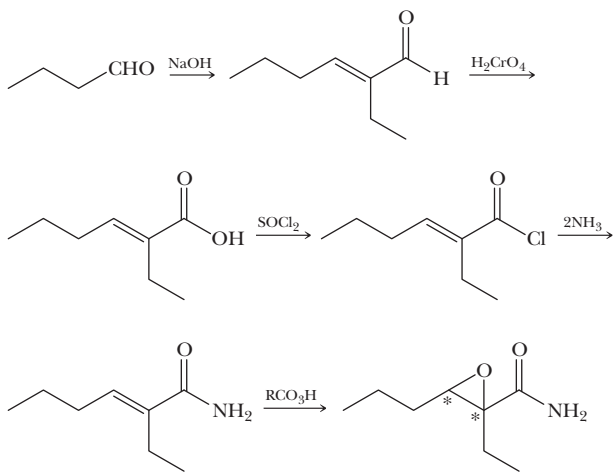
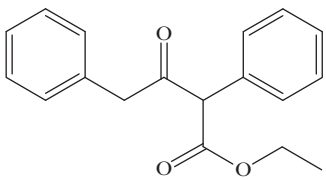


15.25 (a)



(b) 2 stereocenters, 4 stereoisomers possible

15.27 (a)



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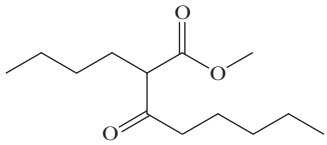

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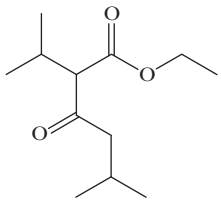

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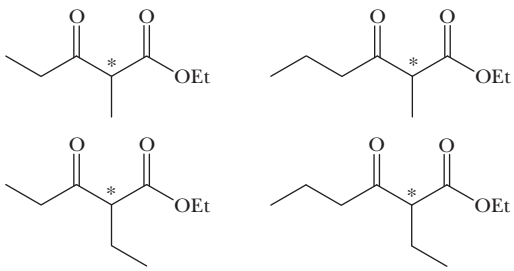

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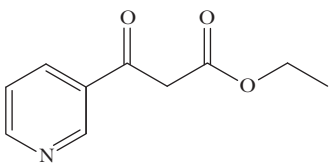
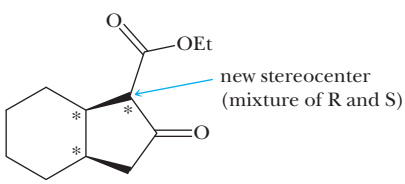


15.33 (a)



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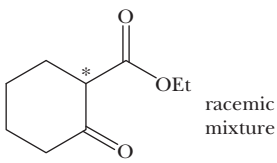
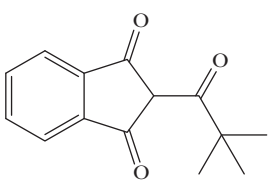
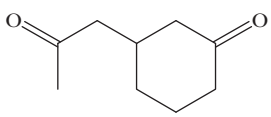


15.35



15.37 (a)



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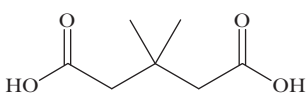
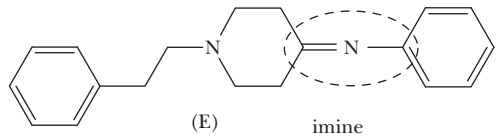


15.39 (a) Ethyl 2-propenoate, Michael addition performed twice

(b) Strong base, Dieckmann reaction, followed by aqueous acid

(c) Saponify the ester with NaOH, treat the carboxylate salt with HCl, and then heat the compound.

(d) Aniline



(e) H_2/Pd

(f) An acid chloride, anhydride, or ester

(g) Achiral because it does not have any stereocenters

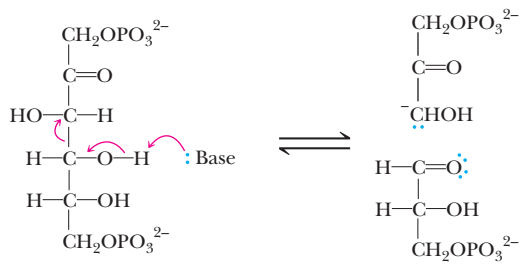
15.41 (a) NaOH, aldol reaction

(b) Heating in NaOH or H_2SO_4

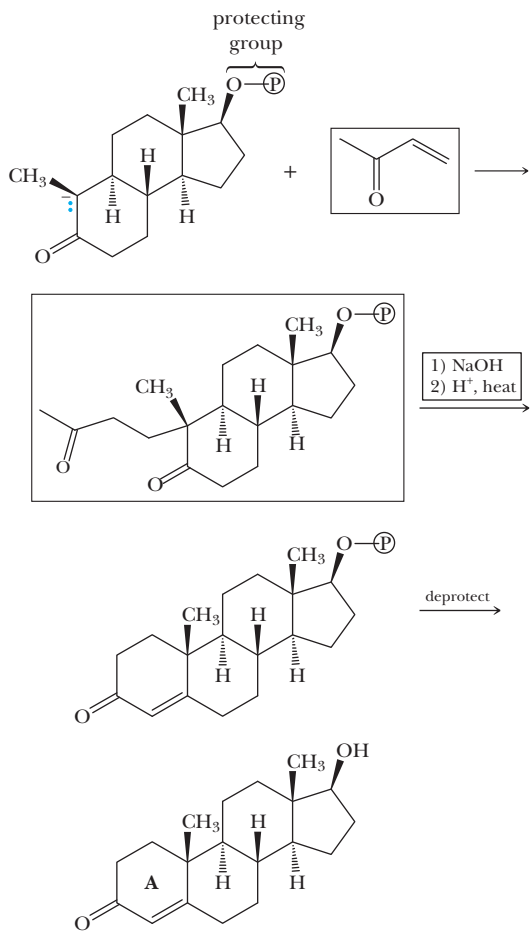
(c) H_2/Pd

(d) Fischer esterification with *p*-methoxycinnamic acid

15.43



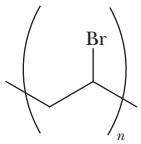
15.45



CHAPTER 16 Organic Polymer Chemistry

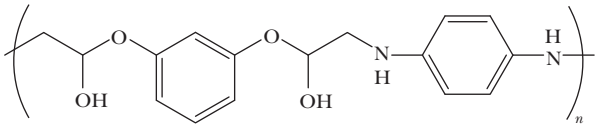
Problems

16.1



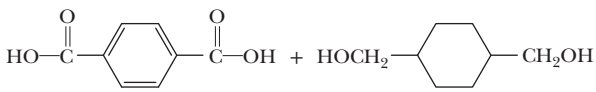
Poly(vinyl bromide)

16.2

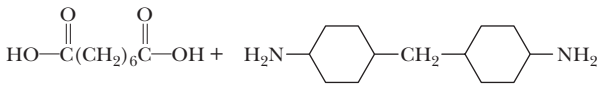


End-of-Chapter Problems

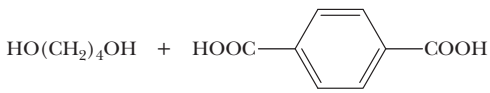
16.3 (a)



(b)



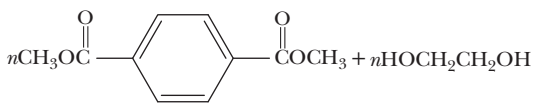
(c)



(d) $HOOC(CH_2)_8COOH + H_2N(CH_2)_6NH_2$

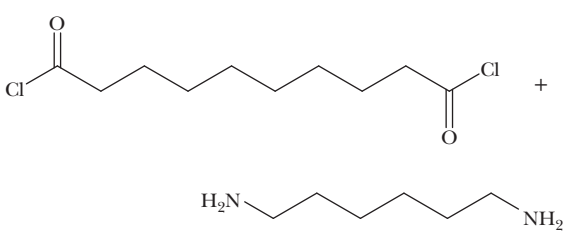
16.5

Poly(ethylene terephthalate) Methanol

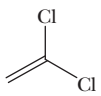


Dimethyl terephthalate Ethylene glycol

16.7



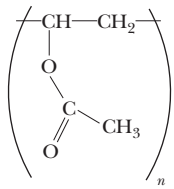
16.9 (a)



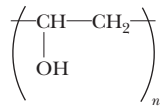
(b)

16.11 The chains are less able to pack together in the solid state.

16.13



Poly(vinyl acetate)



Poly(vinyl alcohol)

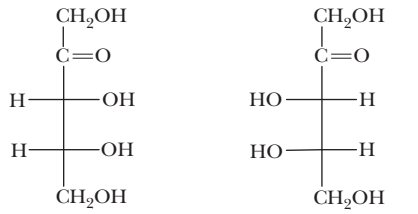
16.15 A and B are the most rigid. C is the most transparent.

16.17 Yes

CHAPTER 17 Carbohydrates

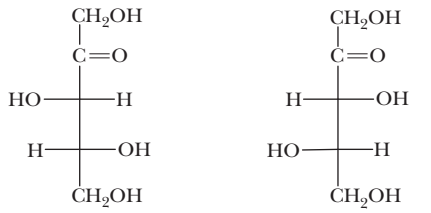
Problems

17.1



D-Ribulose L-Ribulose

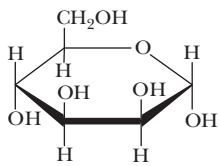
enantiomers



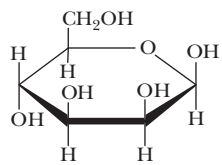
D-Xylulose L-Xylulose

enantiomers

17.2

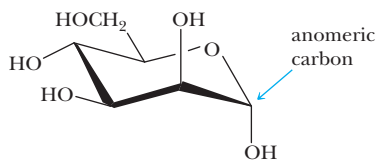


α-D-Mannopyranose (α-D-mannose)

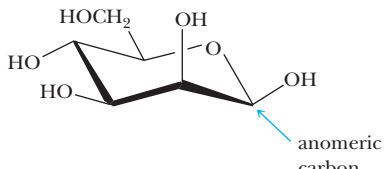


β-D-Mannopyranose (β-D-mannose)

17.3

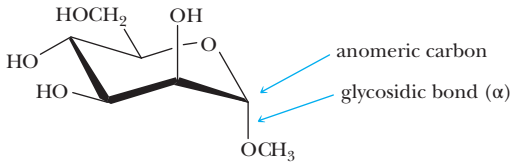


α-D-Mannopyranose

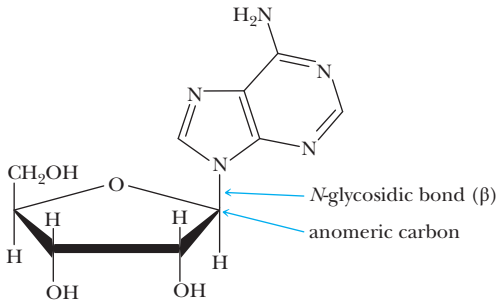


β-D-Mannopyranose

17.4

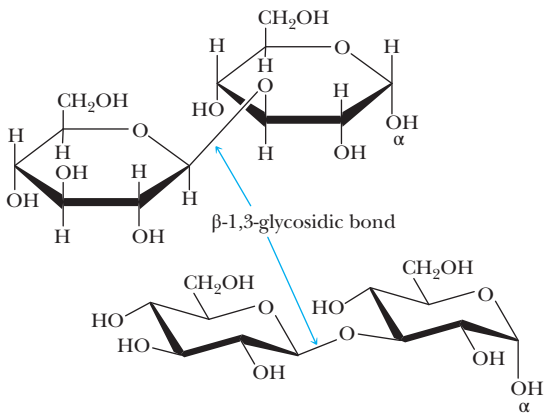


17.5



17.6 Optically inactive, because erythritol is a meso compound

17.7



End-of-Chapter Problems

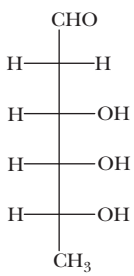
17.9 D-Glucose

17.11 The designations refer to the configuration of the penultimate carbon. If the monosaccharide is drawn as a Fischer projection and the —OH group bonded to this carbon is on the right, the D designation is used; likewise, a monosaccharide is L if the —OH group is on the left.

17.13 (a) and (c) are D-monosaccharides, while (b) and (d) are L-monosaccharides.

17.15 Mono- and disaccharides are polar compounds and are able to participate in hydrogen bonding with water molecules.

17.17

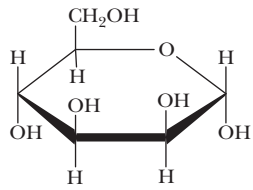


2,6-Dideoxy-D-altrose

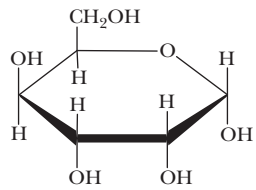
17.19 The α and β designations refer to the position of the hydroxyl (—OH) group on the anomeric carbon relative to the terminal —CH_2OH group. If both of these groups are on the same side of the ring (*cis*), a β designation is assigned. If the two groups are on the opposite side of the ring (*trans*), the monosaccharide is assigned α.

17.21 No, because anomers are compounds that differ only in the configuration of the anomeric carbon. These two compounds are enantiomers.

17.23

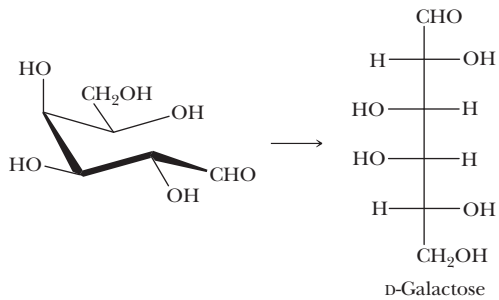


α-D-Mannose



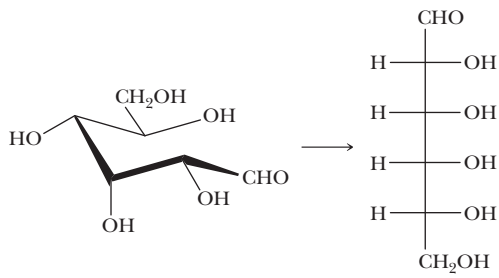
α-D-Gulose

17.25 (a)



D-Galactose

(b)

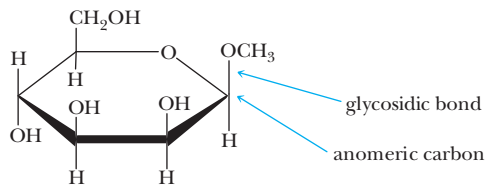


D-Allose

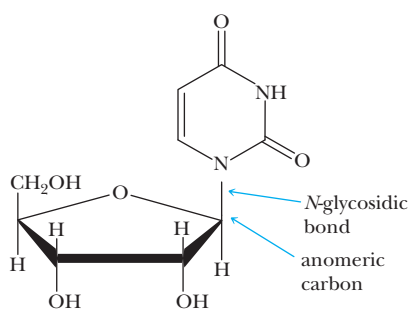
17.27 Mutarotation involves the formation of an equilibrium mixture of the two anomers of a carbohydrate. This process can be detected by observing the change in the optical activity of the solution over time.

17.29 Yes, and the value will change to −52.7° (an equilibrium mixture of α- and β-L-glucose).

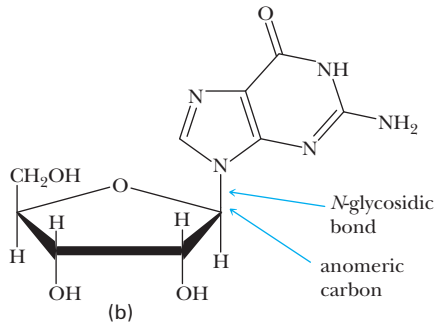
17.31



17.33

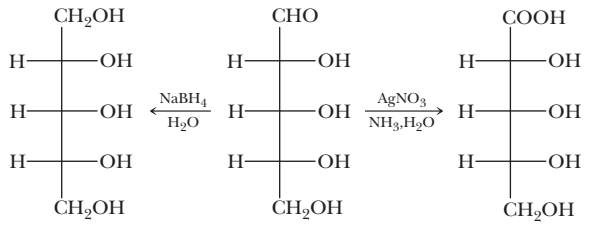


(a)



(b)

17.35



Ribitol
optically inactive
(meso)

D-Ribose

D-Ribonic acid
optically active
(chiral)

17.37 D-Arabinose and D-lyxose yield optically active alditols, while D-ribose and D-xylose yield optically inactive alditols.

17.39 D-Allose and D-galactose

17.41 The bond formed between the anomeric carbon of a glycoside and an —OR group

17.43 No

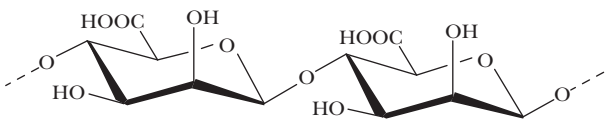
17.45 Maltose and lactose

17.47 (a) No (b) No (c) D-Glucose for both

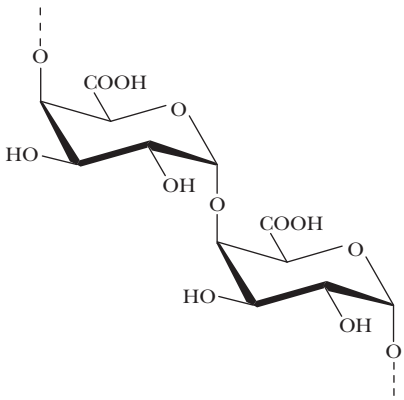
17.49 An oligosaccharide is a short polymer of about 6 to 10 monosaccharides. While there is no definite rule, polysaccharides generally contain more than 10 monosaccharides.

17.51 Both types are composed of D-glucose, and both contain α-1,4-glycosidic bonds. However, amylose is unbranched, while amylopectin contains branches that result from α-1,6- glycosidic bonds.

17.53 (a)



(b)

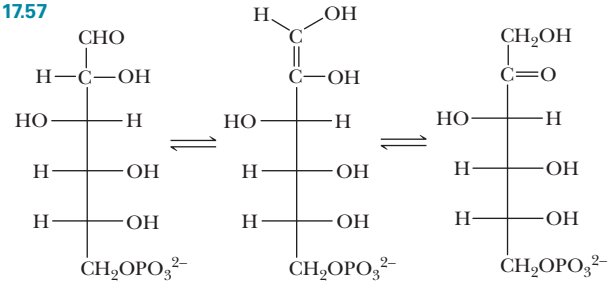


17.55 (a) D-Galactose, D-glucose, and D-glucose

(b) D-Galactose and D-glucose are connected α-(1,4), while the two D-glucose units are connected β-(1,4).

(c) With the two large, nonpolar hydrocarbon chains on the right of the molecule, the molecule is expected to be relatively insoluble in water.

17.57



D-Glucose 6-phosphate

Enediol

D-Fructose 6-phosphate

17.59 First, it is difficult to control the stereochemistry of the glycosidic bond (α or β) because the formation of an acetal (from a hemiacetal) proceeds through an S_N1 mechanism; a mixture of α- and β-glycosidic bonds results. In addition, it is difficult to form only the desired 1,4-linkage, because any one of the hydroxyl groups located on carbons 2, 3, 4, and 6 could be used to form the bond.

CHAPTER 18 Amino Acids and Proteins

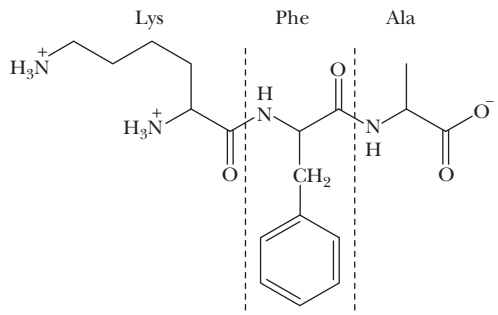
Problems

18.1 (a) Glycine (b) Isoleucine and threonine

18.2 Negative

18.3 Arginine will migrate toward the negative electrode, glutamic acid will migrate toward the positive electrode, and valine will remain at the origin.

18.4 Net charge is +1.



18.5 Trypsin does not hydrolyze any of the choices. Chymostrypsin hydrolyzes (a) and (b)

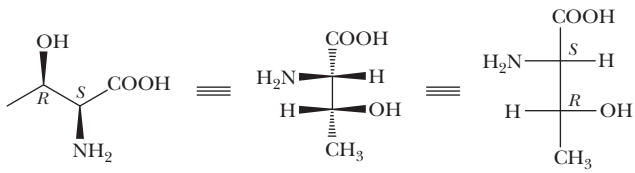
18.6 Ala-Glu-Arg-Thr-Phe-Lys-Lys-Val-Met-Ser-Trp

18.7 Aspartic and glutamic acids

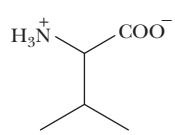
End-of-Chapter Problems

18.9 *S*

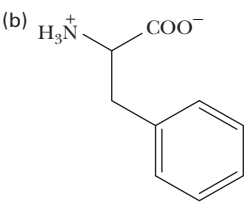
18.11

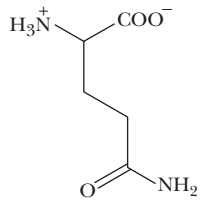


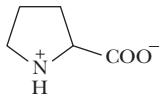
18.13 (a)



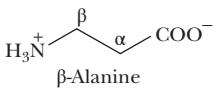
(b)



(c) 

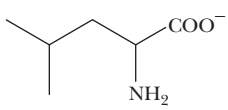
(d) 

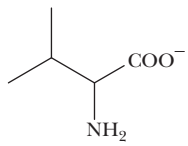
18.15 Arg is a basic amino acid because its side chain is protonated (positively charged) at neutral pH. Lys and His are the other two basic amino acids.

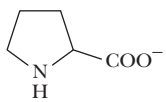
18.17 
β-Alanine

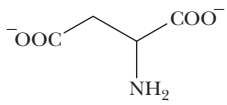
18.19 The biosynthesis of histamine occurs via the decarboxylation of histidine.

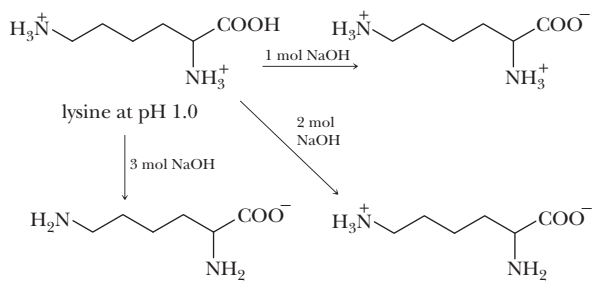
18.21 Serotonin and melatonin are both synthesized from tryptophan. In both cases, the biosynthesis involves a decarboxylation and an oxidation (hydroxylation) of the aromatic ring. In the case of melatonin, there are two more reactions: After the oxidation of the aromatic ring, the hydroxyl group is methylated, and the amino group is acetylated.

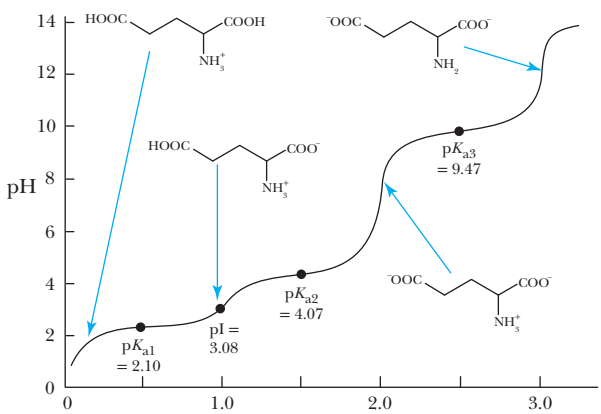
18.23 (a) 

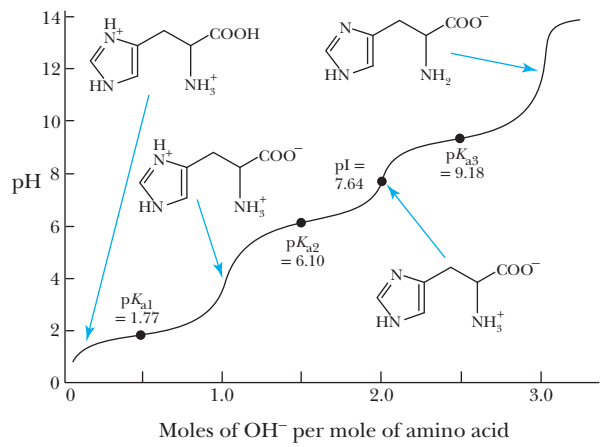
(b) 

(c) 

(d) 

18.25 

18.27 (a) 

(b) 

18.29 With glutamine, its pI value is determined by the pK_a values of the only two ionizable groups, the carboxylic acid (pK_a 2.17) and the α-amino group (pK_a 9.03).

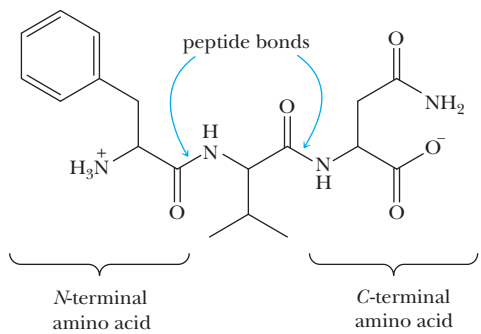
18.31 Guanidine and the guanidino group are very strong amine bases due to the resonance stabilization of the conjugate *acid*, the guanidinium group.

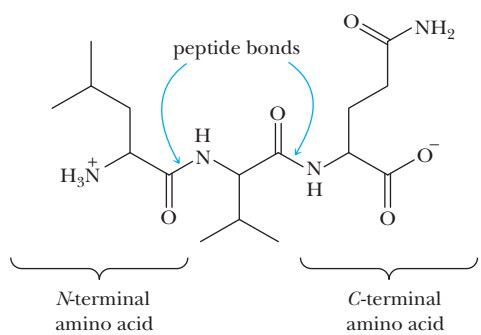
18.33 (a) Cathode (b) Cathode (c) Cathode
(d) Anode (e) Anode (f) Cathode

18.35 Neutral amino acids

18.37 (a) 24 (b) 116,280

18.39 (a) Between residues 1 and 2
(b) Between residues 6 and 7, 10 and 11, 13 and 14, 22 and 23, and 25 and 26
(c) Between residues 12 and 13, 17 and 18, and 18 and 19
(d) Between residues 27 and 28

18.41 (a) 

(b) 

18.43 (a) From the *N*-terminal to the *C*-terminal: glutamic acid, cysteine, and glycine.
(b) The carboxyl group used to form the peptide bond is not that of the α-carboxyl group but rather that of side chain.
(c) Reducing agent

(d) Oxygen is reduced.

$$4G\text{-}SH + O_2 \longrightarrow 2G\text{-}S\text{-}S\text{-}G + 2H_2O$$

18.45 All outside

18.47 Amino acids that are polar, acidic, and basic will prefer to be on the outside of the protein surface, in contact with the aqueous environment to maximize hydrophilic and hydrogen-bonding interactions; these amino acids include Arg, Ser, and Lys. Nonpolar amino acids will prefer to avoid contact with the aqueous environment and turn inward to maximize hydrophobic interactions; these include Leu and Phe.

18.49 No. First, the bulky *sec*-butyl side chains would destabilize an α-helix consisting of only isoleucine. Second, if this α-helix were in an aqueous environment, all the side chains, which are nonpolar, would be on the outside of the helix and exposed to the aqueous environment.

CHAPTER 19 Lipids

Problems

19.1 (a) 3 (b) All are chiral.

End-of-Chapter Problems

19.3 Each triglyceride contains three hydrophobic regions (the hydrocarbon chains of the fatty acids) and three hydrophilic regions (the ester groups).

19.5 Increase

19.7 Animal fat: human Plant oil: olive

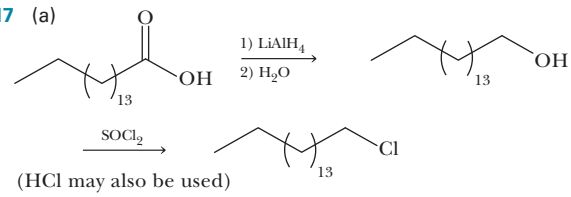
19.9 A very high percentage of the saturated fatty acids have a low molecular weight.

19.11 Hardening refers to the catalytic hydrogenation of the C═C bonds in vegetable oil.

19.13 A good synthetic detergent should have a long, hydrophobic chain and a very hydrophilic head group (either ionic or very polar). In addition, it should not form insoluble precipitates with the ions that are commonly found in hard water, such as Ca^{2+}, Mg^{2+}, and Fe^{2+}.

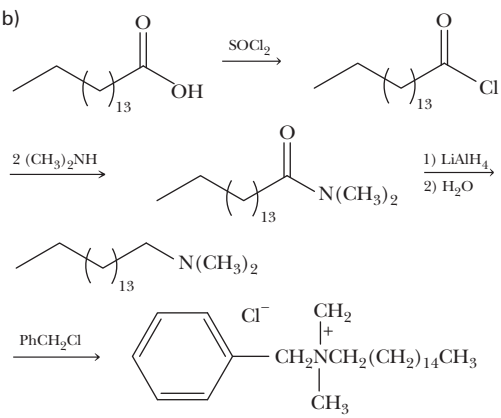
19.15 The detergents are usually anionic.

19.17 (a)

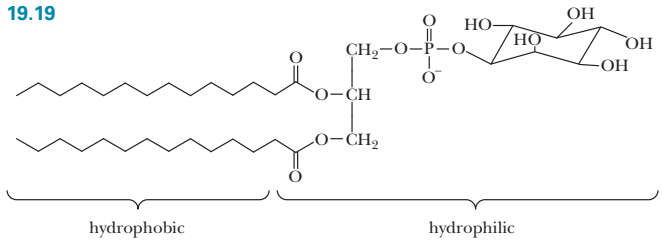


(HCl may also be used)

(b)

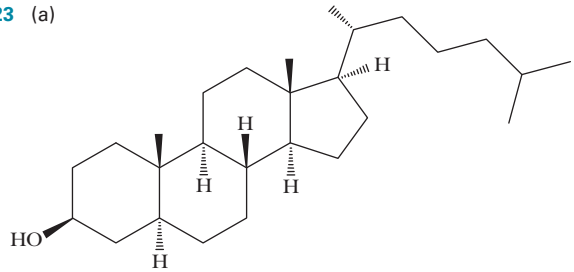


19.19

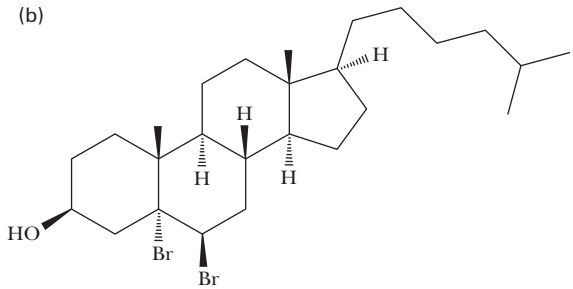


19.21 Unsaturation reduces the melting point of the fatty acids and their ability to pack together.

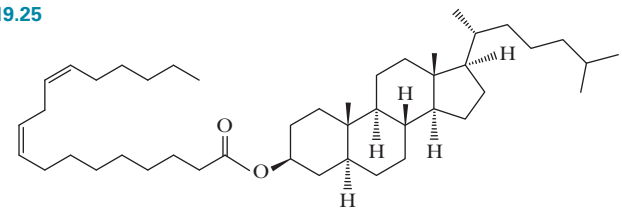
19.23 (a)



(b)



19.25



19.27 Cholic acid is able to act as an emulsifier because it contains both hydrophobic and hydrophilic groups.

19.29 Methandrostenolone has an extra carbon–carbon double bond in ring A and a methyl substituent on carbon 17.

19.31 Four chemical modifications occur when progesterone is converted to estradiol: Ring A is converted into an aromatic ring, the ketone of ring A is converted into a phenol, the methyl group on carbon 10 is removed, and the acetyl group on carbon 17 is replaced by a hydroxyl group.

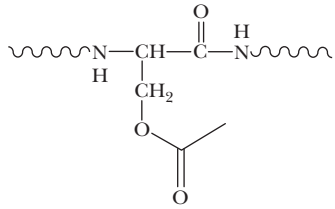
19.33 Unoprostone differs from $PGF_{2\alpha}$ as follows: The double bond between carbons 13 and 14 is reduced, carbon 15 is oxidized from an alcohol to a ketone, and there are two extra carbons (21 and 22) at the end of the molecule.

19.35 16 *cis–trans*

19.37 Not soluble in water or blood plasma, much more soluble in dichloromethane.

19.39 Fluidity increases with increasing temperature.

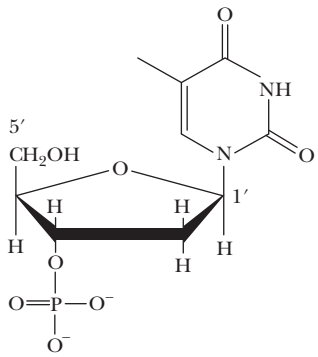
19.41



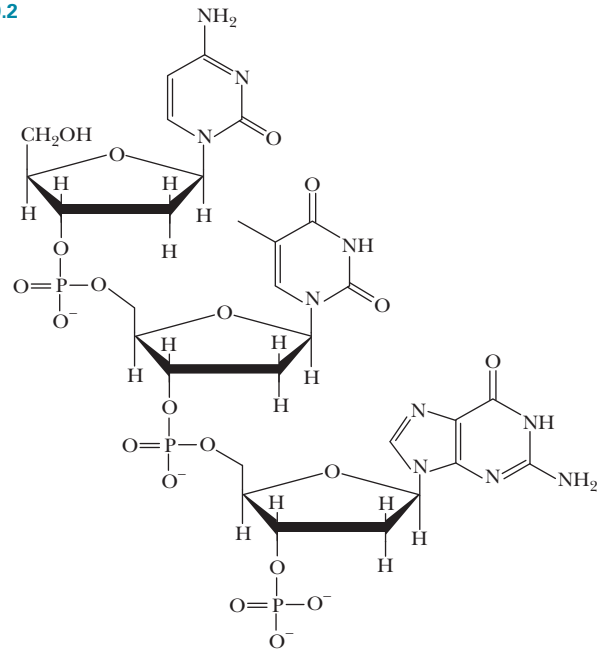
CHAPTER 20 Nucleic Acids

Problems

20.1



20.2



20.3 3′-GGCATGCT-5′

20.4 5′-TGGTGGACGAGTCCGGAA-3′

20.5 (a) 5′-UGC-UAU-AUU-CAA-AAU-UGC-CCU-CUU-GGU-UGA-3′

(b) Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly

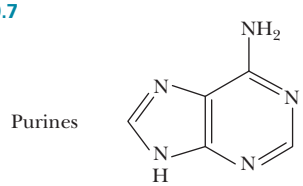
20.6 Restriction endonucleases F*nu*DII and H*pa*II will cleave at the sites indicated below.

5′-ACGTCGGGTCGTCGTCCTCT**CG**–**C**GTGGTGAGCTT**C**–**CGG**CTCTTCT-3′

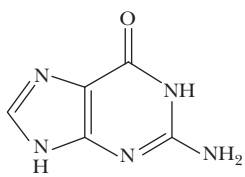
F*nu*DII H*pa*II

End-of-Chapter Problems

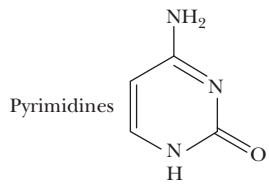
20.7



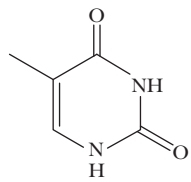
adenine



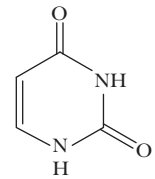
guanine



cytosine



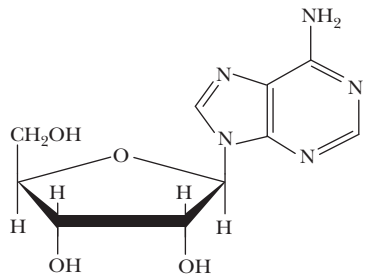
thymine



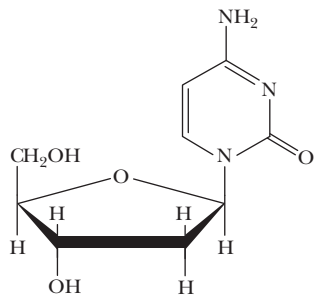
uracil

20.9 A nucleoside consists of only a nucleobase and ribose or 2-deoxyribose. A nucleotide is a phosphorylated nucleoside.

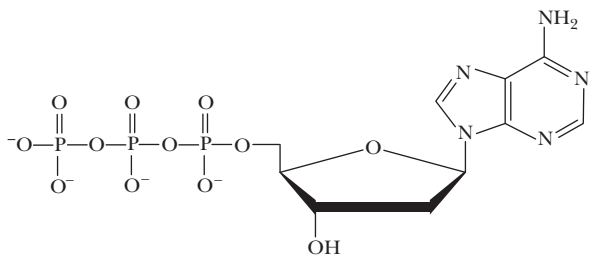
20.11 (a)



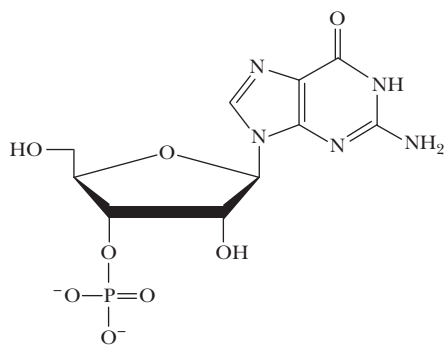
(b)



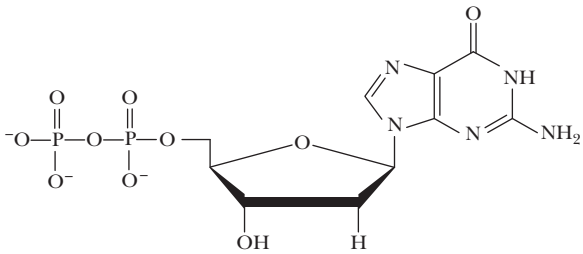
20.13 (a) Net charge of –4



(b) Net charge of –2



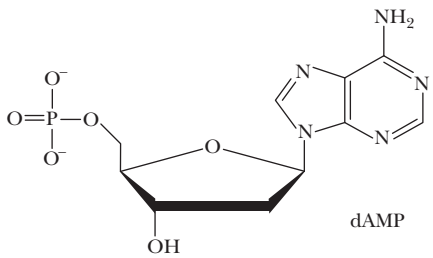
(c) Net charge of –3



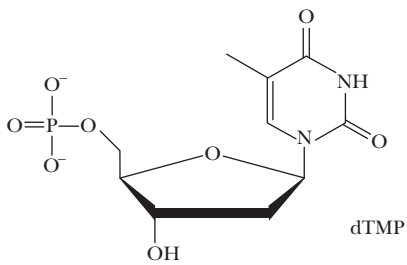
20.15 30.4% T, 19.6% G, and 19.6% C. These agree well with the experimental values found in Table 20.1.

20.17
- DNA consists of two antiparallel strands of polynucleotide that are coiled in a right-handed manner and arranged about the same axis to form a double helix.
- The nucleobases project inward toward the axis of the helix and are always paired in a very specific manner, A with T and G with C. (By projecting the bases inwards, the acidlabile *N*-glycosidic bonds are protected from the surrounding environment.)
- The base pairs are stacked with a spacing of 3.4 Å between them.
- There is one complete turn of the helix every 34 Å (ten base pairs per turn).

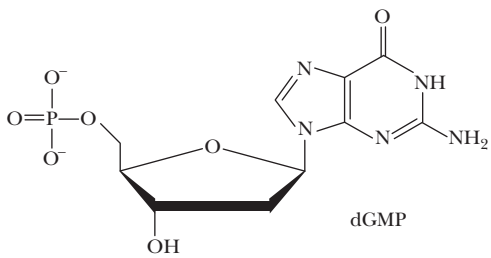
20.19 The nucleotides are 2-deoxyadenosine 5′-monophosphate (dAMP), 2-deoxythymidine 5′-monophosphate (dTMP), 2-deoxyguanosine 5′-monophosphate (dGMP), and 2-deoxycytidine 5′-monophosphate (dCMP).



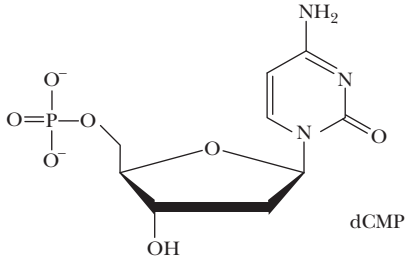
dAMP



dTMP



dGMP



dCMP

20.21 The nucleobases, which are hydrophobic, are pointed inward. This minimizes their contact with water on the outside of the helix and also allows them to stack via hydrophobic interactions.

20.23 Chemically, they are all polymers of ribonucleotides. Functionally, mRNA is a carrier of protein-sequence information, tRNA carries amino acids for protein synthesis, and rRNA is a component of ribosomes.

20.25 The only difference between T and U is the absence of a methyl group in U. The absence of this methyl group has no impact on hydrogen bonding.

20.27 mRNA

20.29 3′-AGUUGCUA-5′

20.31 There are 20 amino acids that are specified by the genetic code and with three nucleotides, 64 different sequence combinations are possible.

20.33 Stop codons

20.35 3′-TGGCAATTA-5′

20.37 More than one codon can code for the same amino acid.

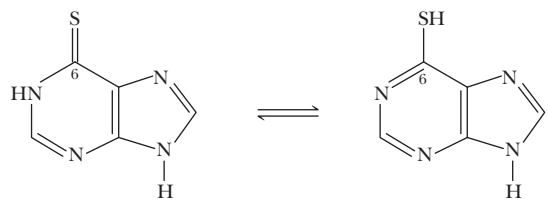
20.39 Both Phe and Tyr are structurally similar, except that Tyr contains a hydroxyl group on the aromatic ring. The codons for Phe are UUU and UUC, while those for Tyr are UAU and UAC; the codons for the two amino acids differ only in the second position.

20.41 The last base in the codons for Gly, Ala, and Val is irrelevant. Other codons in which the third base is irrelevant include those for Arg (CGX), Pro (CCX), and Thr (ACX).

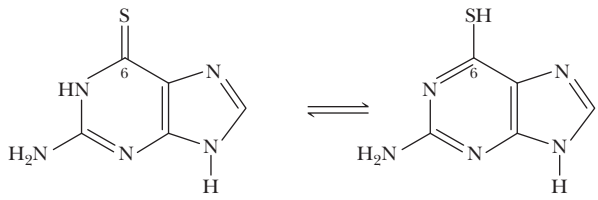
20.43 With the exception of Trp and Gly, all codons with a purine in the second position code for polar, hydrophilic side chains.

20.45 Each amino acid requires one codon (three nucleotides). Therefore, 3 × 141 = 423 bases are required for the amino acids alone, plus another three for the stop codon, giving a total of 426 bases.

20.47



6-Mercaptopurine



6-Thioguanine

20.49 (a) In the α-helices of proteins, the repeating units are amino acids that are linked by peptide (amide) bonds, whereas the repeating units in DNA are 2′-deoxy-D-ribose linked via 3′,5′-phosphodiester bonds.

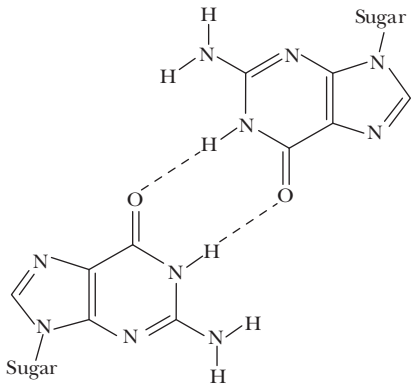
(b) The R groups in the α-helices of proteins point outward from the helix, whereas the nucleobases in the DNA double helix point inward and away from the aqueous environment of the cell.

20.51 (a) Cordycepin is missing the 3′-OH group, so it acts as a chain terminator.

(b) The trichlorinated benzimidazole fragment mimics a purine base. This compound likely interferes with RNA polymerase, the enzyme that transcribes RNA from DNA.

(c) It is an analog of adenosine and likely interferes with the enzymes involved in nucleic acid synthesis.

20.53



CHAPTER 21 The Organic Chemistry of Metabolism

Problems

21.1 Neither

21.2 Blood pH decreases

End-of-Chapter Problems

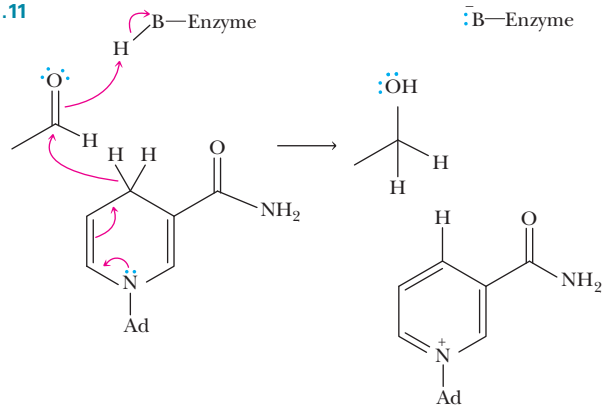
21.3 Aspartic acid and glutamic acid; conjugate acids of histidine, lysine, and arginine; and serine and cysteine

21.5 One coenzyme required for glycolysis (the oxidation steps) is nicotinamide adenine dinucleotide (NAD^+), and it is derived from the vitamin niacin.

21.7 6

21.9 Four moles of ethanol and four moles of CO_2

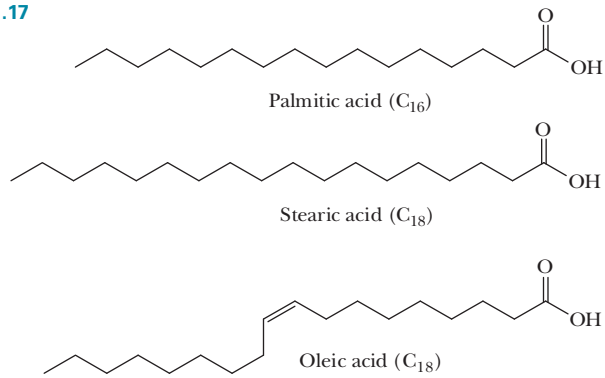
21.11



21.13 Hydrogen added to carbonyl carbon

21.15 3 and 4

21.17



21.19 FAD (riboflavin), NAD^+ (niacin), and coenzyme A (pantothenic acid)

21.21 To oxidize the two carbon atoms of the acetyl group in acetyl-CoA into carbon dioxide

21.23 None of the intermediates involved in the cycle are destroyed or created in the net reaction.

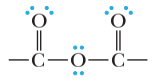
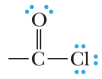
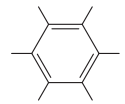
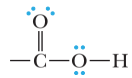
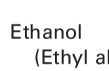
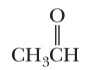
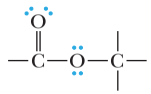
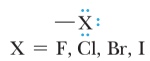
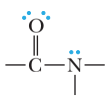
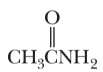
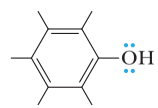
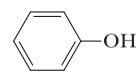
21.25 (a) $C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O$

(b) $C_{57}H_{104}O_6 + 80O_2 \longrightarrow 57CO_2 + 52H_2O$ RQ = 0.71

(c) Decrease:
$C_2H_6O + 3O_2 \longrightarrow 2CO_2 + 3H_2O$ RQ = 0.67

21.27 Carbons 1 and 6 of glucose become the methyl groups of acetyl-CoA. The even-numbered carbon atoms of palmitic acid become the methyl groups of acetyl-CoA.

Some Important Organic Functional Groups

	Functional Group*	Example	IUPAC Name		Functional Group*	Example	IUPAC Name
Acid anhydride			Ethanoic anhydride (Acetic anhydride)	Amine, tertiary		$(CH_3CH_2)_3N$	Triethylamine
Acid chloride			Ethanoyl chloride (Acetyl chloride)	Arene			Benzene
Alcohol		CH_3CH_2OH	Ethanol (Ethyl alcohol)	Carboxylic acid			Ethanoic acid (Acetic acid)
Aldehyde			Ethanal (Acetaldehyde)	Disulfide		CH_3SSCH_3	Dimethyl disulfide
Alkane	--------	CH_3CH_3	Ethane	Ester			Methyl ethanoate (Methyl acetate)
Alkene		$CH_2{=}CH_2$	Ethene (Ethylene)	Haloalkane		CH_3CH_2Cl	Chloroethane (Ethyl chloride)
Alkyne		$HC{\equiv}CH$	Ethyne (Acetylene)	Ketone			Propanone (Acetone)
Amide			Ethanamide (Acetamide)	Phenol			Phenol
Amine, primary		$CH_3CH_2NH_2$	Ethylamine	Sulfide		CH_3SCH_3	Dimethyl sulfide
Amine, secondary		$(CH_3CH_2)_2NH$	Diethylamine	Thiol		CH_3CH_2SH	Ethanethiol (Ethyl mercaptan)

* Where bonds to an atom are not specified, the atom is assumed to be bonded to one or more carbon or hydrogen atoms in the rest of the molecule.

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