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Aromaticity in Heterocyclic Compounds

Volume Editors:
Tadeusz M. Krygowski · Michał K. Cyrański

With Contributions by

M. A. R. Matos · I. Alkorta · A.T. Balaban
Z. Benkö · J. Elguero · M. Giurg · T. Gracza,
A. Krutošíková · L. Latos-Grażyński · Joel F. Liebman
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Preface

Aromaticity is a notion that appeared in the mid-nineteenth century to differentiate between unsaturated hydrocarbons and formally unsaturated benzene [1–3]. At the end of the nineteenth century it seemed that cyclicity was a necessary condition for differentiation between the two, but at the beginning of the twentieth century it turned out that the above assumption was not correct because cyclooctatetraene exhibited typical properties known for polyenes [4]. The essential property of benzene-like compounds, often identified with aromatic compounds, was low reactivity. Hence thermodynamic stability was defined as resonance energy [5, 6] and was the first quantitative measure of aromaticity. Many theoretical approaches were proposed later to estimate this quantity, and now the criterion is often considered to be the most fundamental [7]. Almost at the same time, magnetic susceptibility was used to describe aromaticity [8, 9]. Consequently, many concepts based on magnetism were developed, probably the most effective in assessment of aromaticity being nucleus independent chemical shift (NICS) [10] or Fowler's maps of ring currents [11]. The criterion served Schleyer as a basis for a definition of aromaticity: "Compounds which exhibit significantly exalted diamagnetic susceptibility are aromatic. Cyclic delocalisation may also result in bond length equalization, abnormal chemical shifts and magnetic anisotropies, as well as chemical and physical properties which reflect energetic stabilisation"[12]. For a long time bond length alternation has been used as an indication of non-aromaticity, but a quantitative approach based on this criterion was only invented by A. Julg in 1967 [13]. This idea was extended in 1972 [14] and can be used to estimate both the local and global aromaticity of molecules. Actually there are many quantitative descriptors assumed to be, or even named as, aromaticity indices. To make the situation clearer, widely acceptable criteria were reported in Tetrahedron: [15]

A cyclic π-electron compound is aromatic if there appears a measurable π-electron delocalization in the ground state of the molecule. This is associated with:

1. An increase of stability related to the system without cyclic π–electron delocalization
2. Intermediate and unaltered bond lengths that are close to the mean value of the length for the typical single and double bonds
3. Inducing π-electron ring current when the molecule is exposed to the external magnetic field

An additional criterion, in our opinion a very important one, but which is not a property of the ground state, is reactivity. Generally, aromatic compounds undergo electrophilic substitution reactions (aromatic substitution) more easily than addition, which is often expressed as a typical tendency of these kinds of systems to retain their initial π-electron structure [16, 17].

Since aromaticity has been recognized as a multidimensional phenomenon [18, 19] two modern definitions take into account all the above-listed features. Krygowski, Katritzky et al. [15] proposed:

> Those cyclic π-electron systems which follow all the features of aromatic character (including reactivity) are aromatic, while those which follow some but not all of them are partly aromatic.

In turn, Chen, Schleyer et al. [20] proposed that:

> Aromaticity is a manifestation of electron delocalization in closed circuits, either in two or in three dimensions. This results in energy lowering, often quite substantial, and a variety of unusual chemical and physical properties. These include a tendency toward bond length equalization, unusual reactivity, and characteristic spectroscopic features. Since aromaticity is related to induced ring currents, magnetic properties are particularly important for its detection and evaluation.

So far, aromaticity has no unique and widely accepted definition. Despite this shortcoming, or maybe perversely due to it, the phenomenon has been a subject of an ever-increasing number of intense studies. What is the reason for that? The concept, although theoretical in nature, is of immense practical importance [15]. Its impact on modern organic chemistry can hardly be overestimated. Let the facts speak for themselves. Two thematic issues of Chemical Reviews have been devoted to aromaticity in the last decade [7, 20–53]. The 2001 May volume of the journal, which explicitly dealt with the topic [21–39], was recognized as being extremely successful. The Association of American Publishers awarded that work the Best Single Issue Prize in the "Professional and Scholarly Publishing Division" [40]. The 2005 October issue, dedicated more generally to electron delocalization in sigma and pi sense, was a consequence of that success [7, 20, 40–53]. In the meantime two excellent single review articles appeared: "Aromaticity as a cornerstone of heterocyclic chemistry" [54] and "Aromaticity of polycyclic conjugated hydrocarbons" [55]. Soon after, the December 2006 thematic issue of Chemical Reviews on "Designing the molecular world" [56] contributed with a number of highly recommended articles on the subject: "Twisted acenes," [57] "Aromatic molecular-bowl hydrocarbons: synthetic derivatives, their structures, and physical properties," [58] "Heterofullerenes," [59] and "Renaissance of annulene chemistry" [60]. Conferences, symposia, and workshops organized all over the world gathered scientists representing different fields of science and having different experience and skills. Let us note just few of those events: European Science Foundation Exploratory Workshop: New Perspectives on Aromaticity, organized in Exeter (2004) [61–74] or ISNA – International Symposium on Novel Aromatic Compounds [75, 76], arguably the most important and influential conference in the field, which is now organized every two years, with the next meeting to be held in Luxembourg 2009 [75, 77–94].

The question has been posed: how does aromaticity change if in a carbocyclic π-electron system one or if a few CH units are replaced by heteroatom(s)? What can be expected? Undoubtedly, these kinds of changes are associated with changes in electron structure due to different electronegativity, e.g., $\chi(Csp^2) = 2.75$ as compared with $\chi(Nsp^2) = 3.94$, $\chi(B) = 2.04$, $\chi(S) = 2.56$, $\chi(P) = 2.19$ (Tables 6.5 and 6.7 in [95]) and should be reflected in π-electron delocalization. In consequence, many properties typical of aromaticity may change, sometimes dramatically.

This volume consists of seven contributions, which present various kinds of heteroaromatic compounds and various aspects of their chemistry, physical chemistry, and structural chemistry. The aromaticity of these compounds is, however, the crucial point of these contributions and makes this notion more understandable.

The first chapter by M. A. R. Matos and Joel F. Liebman deals with recent advances in the experimental thermochemistry of nitrogen, oxygen, and sulfur derivatives of indane and indene. Analyses are based on enthalpies of formation in gaseous phase, and are mostly concerned with aromatic stability and strain destabilization in cases where molecules contain a saturated fragment. At the end there is a table of enthalpies of formation of indanes and related dibenzoannulated species. The table also presents enthalpy differences between indane/indene analogs and their five-membered fragments, which are fused to benzene. The differences are a rough estimation of enthalpy of formation of benzene but also contain the contribution resulting from conjugation between the benzene ring and a fused fragment.

Chapter 2 by László Nyulászi and Zoltán Benkő deals with the chemistry and physical organic chemistry of aromatic phosphorus heterocycles and is divided into four subchapters dealing with three- , four-, five-, and six-membered rings, in which there may be more than one phosphorus atom. The chapter begins with a clear presentation of the electronic structure that phosphorus may achieve in molecules with CP bonds. For cyclopentadiene and phosphole eight aromaticity indices are collected. Almost all of them indicate that phosphole is more aromatic than cyclopentadiene. It is also shown that even small structural effects (substituent, bonding modes) can have a substantial impact on the chemistry of the reported systems.

Chapter 3 by Marcin Stępień and Lechosław Latos-Grażyński deals with π-electron delocalization in relation to tautomerism and chemical properties in porphyrines and porphyrinoids. An important and very interesting problem discussed here is that for the title systems aromaticity may be concerned either locally (for one or a few rings) or for a whole macrocycle. The body of the chapter is based on analyses of ^{1}H NMR and UV/Vis spectroscopies and takes into account the relations between π-electron delocalization and tautomeric equilibria.

In the next chapter by Ibon Alkorta and José Elguero, applying computational approaches presents interrelations between aromaticity and chemical and physicochemical properties of heterocycles. The following problems and properties are considered: tautomerism, conformation analysis, acid–base equilibria, H-bonding and proton transfer, energetics, reactivity, IR-, NMR-, and MW-spectroscopies. At the end is a discussion of problems related to supramolecules and macrocycles.

Alexandru T. Balaban in the fifth chapter considers six-membered rings with one heteroatom and even some metallobenzene derivatives. Thus, analysis of the

role of heteroatom becomes more precise. There is a comparison of the aromaticity of 18 charged and neutral species with indicated values of NICS. Since the formation of the title compounds results from replacement of a CH fragment by an appropriate heteroatom or its substituted derivative, the original "aromaticity constants" (that may also be considered "relative electronegativities" of these groupings) of the first row atoms are presented.

Alžbeta Krutošíková and Tibor Gracza present in the sixth chapter recent studies of heteroanalogs of pentalene dianion in which the CH fragment is replaced by O, NH, S, Se, and Te atoms. Mostly the syntheses of these kinds of compounds or their derivatives are presented, but the distinction between particular representatives is well outlined.

Chapter 7, by Jacek Młochowski and Mirosław Giurg deals with aromatic and related selenaheterocycles and their applications. The chapter presents firstly the chemical properties of selenaheterocyclic rings: tautomerism, reactions on the carbon atom and on the heteroatom, and finally ring transformations. Next are presented the syntheses of selenaheterocyclic compounds like selenphanes, isoselenazoles, selenazoleds, selenadiazoles, and selenoporphyrines. Finally, an outline of the applications of selenaheterocycles is presented.

The role of the concept of aromaticity in the field of heterocyclic chemistry can hardly be overestimated. It is considered to be a cornerstone of heterocyclic chemistry [54]. We believe that the presented selection of recent achievements in the field supports this opinion very well.

Warsaw, Summer 2008

Tadeusz Marek Krygowski
Michał Ksawery Cyrański

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Experimental Thermochemistry of Heterocycles and Their Aromaticity: A Study of Nitrogen, Oxygen, and Sulfur Derivatives of Indane and Indene

M. Agostinha R. Matos and Joel F. Liebman

Abstract In the current chapter the study of aromaticity is limited to thermochemical concerns (just to those derived from enthalpies of formation in gaseous phase) and to heterocycles containing nitrogen, oxygen, and sulfur as found in a ring (or collection of rings) for which there is unbroken π bonding between the constituent atoms.

We will take a semiempirical approach using numerous molecules, models, assumptions, and estimates rather than doing new calorimetric experiments and/or quantum chemical calculations. Indeed, we will also test what is probably the simplest assumption – that (4n + 2) π electrons found within a conjugated ring species is expected to result in enhanced stability and that this compound is called "aromatic." We will consider the dihydroindene (indane) skeleton composed of a benzene ring fused to a nonaromatic five-membered ring that lacks additional double bonds, and will use this carbocyclic hydrocarbon with X = Y = Z = CH_2 as a paradigm for many heterocyclic derivatives for which the possible aromaticity is of relevance to the current chapter. Similarly we use indene with {–X–Y–} = {–CH=CH–}, Z = CH_2 for a variety of unsaturated heterocycles of interest here.

Keywords aromaticity, indane, indene, nitrogen-containing heterocycles, oxygen-containing heterocycles, sulfur-containing heterocycles, thermochemistry

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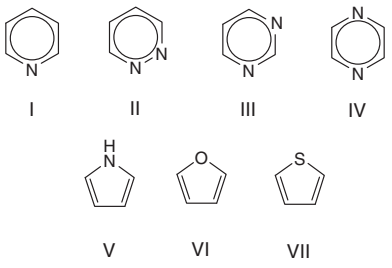
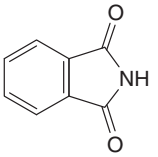
Contents

1 Introduction: Composition and Compounds

Aromaticity (and antiaromaticity) is a key, multifaceted, and elusive molecular property. There are now three standard enunciated "tripartite" criteria (energy, magnetic, and structure). In the current chapter the study of aromaticity is limited to thermochemical concerns (just to those derived from enthalpies of formation) and to heterocycles containing nitrogen, oxygen, and sulfur as found in a ring (or collection of rings) for which there is unbroken π bonding between the constituent atoms. This includes species such as pyridine (**I**) and the isomeric diazines: pyridazine (**II**), pyrimidine (**III**), and pyrazine (**IV**). Species such as pyrrole (**V**), furan (**VI**), and thiophene (**VII**) likewise qualify.



Explicitly included are species with carbonyl (>CO) groups such as the isomeric phthalimide (**VIII**) and isatin (**IX**), and with thiocarbonyl (>CS) groups such as the isomeric benzo-1,2-dithol-3-thione (**X**) and benzo-1,3-dithiol-2-thione (phenylene trithiocarbonate) (**XI**). Conversely, species with the isoelectronic >BF (and the related >BH) are ignored. Thus the question of the aromaticity in carboranes never arises in this chapter, even had we been explicitly interested in three-dimensional aromaticity (another issue we will ignore here).



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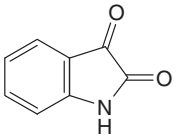

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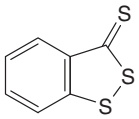
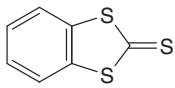


X

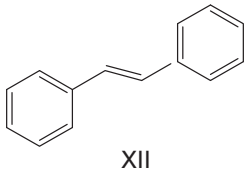


XI

2 Applications of "Isomeric" and "Experimentally Realized Dewar–Breslow" Reasoning

2.1 Benzene

It is to be acknowledged that many of the logical approaches to the evaluation of aromatic character that work for carbocycles are absent in this chapter on heterocycles, as attention is paid only to thermochemical information from the experimental (i.e., noncalculational theoretical literature), with occasional accompaniment from seemingly necessary estimates. As such, many of our comparisons derived from "isomeric" [1–3] and "experimentally realized Dewar–Breslow" [4–6] reasoning, which work so well for carbocycles and even one-ring heterocycles, are generally without use for the heterocycles of interest in this study. For example, benzene may be interrelated to the hydrogenated cyclohexene and cyclohexane along with, quite sensibly, 1,3-cyclohexadiene; with the ("isotoluene") 5-methylene-1,3-cyclohexadiene; with 1,3,5-hexatriene (see the diene/polyene review [7]), or perhaps reluctantly with its diphenylated counterpart, stilbene (**XII**) (the *trans*-isomer chosen because of its planarity and greater stability).


XII

Benzene may also be interrelated with the simplest acyclic double bond-containing organic compound, ethylene, as well as with (*Z*)- and (*E*)-2-butene,

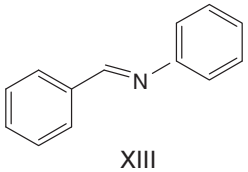
the simplest acyclic organic compound where the double bond is flanked by two carbon–carbon single bonds rather than only carbon–hydrogen bonds. Toluene, which to us is the simplest substituted plausibly aromatic carbocycle, can be related to either isomer of methylenecyclohexadiene. Indeed, the methyl group is innocuous enough that this comparison serves us well for understanding the aromaticity of benzene. Ion chemistry has given us the enthalpy of formation of the *o*-isotoluene needed for the isomerization approach [8]. Likewise this discipline has given us values for *p*-isotoluene [8, 9], but these are in significant disagreement. Hydrogenation calorimetry gives us the enthalpy of formation of both (*Z*)- and (*E*)-1,3,5-hexatriene. The latter in an inert hydrocarbon solvent [10] is to be trusted more than the nearly identical value from the earlier study in acetic acid [11] since solvent effects may be ignored in the former. Both results can be trusted more than the value from a still-earlier combustion calorimetric investigation [12]. This arises from the general observation that combustion calorimetry is prone to greater experimental uncertainty in its measurement than hydrogenation calorimetry. More precisely, when both measurements can be performed, the final enthalpy of hydrogenation is so much smaller than that of combustion. A given percent error because of impurities or any other source of mismeasurement results in a smaller numerical error [13]. This is especially the case for reactive or unstable species, such as the easily oxidized and easily polymerized triene.

2.2 Pyridine

This chapter is devoted to heterocycles, not carbocycles. By analogy to benzene, should we wish to study reasoning derived from isomeric and Dewar–Breslow approaches, we would thus turn to the isoelectronic, isovalent, π-conjugate pyridine, I. This species is plausibly the simplest heterocycle to discuss from the vantage points of aromaticity and thermochemistry. This species would naturally be related to its hydrogenated species, but enthalpy of formation data is limited in the experimental thermochemical literature to the hydrogenated $\Delta^{1,2}$- [14] and $\Delta^{3,4}$-piperideine and piperidine (the reference for the second ($\Delta^{3,4}$-) piperideine and for piperidine is Pedley [15]; from now on all unreferenced data may be assumed to come from this archival source). The enthalpy of formation remains unknown for both 1,2- and 1,4-dihydropyridine and for both of their corresponding derivatives save that of a nineteenth century measurement for a highly substituted species, 3,5-dicarbomethoxy-2,4,6-trimethyl-1,4-dihydropyridine in the solid phase [16] (as cited by [17]). However, equilibration studies show the *N*-methyl derivative of 1,2-dihydropyridine to have a higher enthalpy by 10 kJ mol^{-1} than its 1,4-isomer [18]. Relatedly, hydride transfer studies for a variety of substituted phenyl-1, 2-dihydropyridines show these species to be ca. 6 kJ mol^{-1} less stable than their corresponding 1,4-isomer [19]. We start with plausibly the simplest substituted heterocycle, methylpyridine, to enable understanding of pyridine itself. But, we

must ask: "which one?" since there are enthalpy of formation data available for each of the three so-called picolines. The three values are close enough, with only a 7 kJ mol^{-1} spread, that we can content ourselves with any of them. However, there is no directly measured enthalpy data for the corresponding methylene-dihydropyridines (aza-cyclohexadienes). Estimates from solution phase basicity (pK_a) determinations suggest that pyridine has 84 and 75 kJ mol^{-1} more resonance stabilization than 4-methylene-1,4-dihydropyridine and 2-methylene-1,2-dihydropyridine, respectively [20].

We acknowledge that although thermochemical estimates will occasionally be used in the current study, we forego the results from quantum chemical calculations largely in the name of brevity. We are forced to use benzalaniline (**XIII**), there being no enthalpy of formation known for its acyclic counterpart CH_2=CH–CH=N–CH=CH_2, for either of its isomers CH_2=CH–CH=CH–CH=NH and CH_2=CH–CH=CH–N=CH_2, nor an unequivocal measured value for CH_2=NH or any of its methylated derivatives (see the summaries of imine thermochemistry [21, 22]). We additionally note that benzalaniline, taken as its *trans*-isomer like its hydrocarbon counterpart stilbene (**XII**), is a conventional,



XIII

convenient organic compound for the thermochemically inclined investigator [23, 24]. We recall the multidecade-old dialogue between one of the authors (JFL) and the highly respected, recently deceased ion chemist Sharon G. Lias [25] on the feasibility of studying a compound of mutual interest:

SGL to JFL: "My idea of synthesis is opening a bottle."
JFL to SGL "As a theorist, my idea of synthesis is convincing you to open that bottle."

While many other thermochemists are more willing to indulge in organic synthesis (such as the other author MARM), it is nonetheless unequivocal that ease of acquiring, purifying, and handling a compound of interest is a rate-determining step for many researchers. We also note that, even here, our thermochemical archive refers to two measurements of its enthalpy of formation that differ by ca. 15 kJ mol^{-1}.

2.3 Pyrrole, Furan and Thiophene

The second simplest heterocycle, or should we say set of heterocycles, are the six-π electron pyrrole (**V**), furan (**VI**), and thiophene (**VII**). While all tetrahydrogenated derivatives are known to the thermochemist, only the dihydrofuran and dihydrothiophene also are. Both the 2- and 3-methylthiophenes have been studied, and not surprisingly their enthalpies of formation are very close. However, no such

values are available for any gaseous methylated pyrroles or furans (save 2,5-dimethylpyrrrole [15] and 2,5-dimethylfuran [26]) and in no case are the *exo*-methylene derivatives needed for the isomerization method. The enthalpies of formation of divinyl ether and sulfide are known, but not of divinylamine. The three diphenyl amine, ether, and sulfide derivatives have all been studied and the use of their enthalpies of formation gives us confidence in the experimental Dewar–Breslow approach [4–6].

However, measured data is missing for numerous cases of putative aromatic species with multiple heteroatoms, a situation only worse for the aforementioned approaches to thermochemical understanding of the aromaticity of these more general heterocycles. We are not ready to relinquish this study to computational theorists and so we will present yet other models in this chapter. While these models are not universal, i.e., not all comparisons can be made for all heterocycles, they interleave in that we may use more than one comparison for some heterocycles and derive inequalities and bounds for their varying degrees of aromaticity.

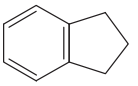
2.4 Is There a Unifying Model?

Reiterating, our analysis will be piecemeal in that we will offer no unifying method or mode of understanding the thermochemistry of aromatic heterocycles: in that way, we are taking a semiempirical approach using numerous molecules, models, assumptions, and estimates rather than doing new calorimetric experiments and/or quantum chemical calculations. Indeed, we will also test what is probably the simplest assumption – that $(4n + 2)\ \pi$ electrons found within a ring species is expected to result in enhanced stability, and that this compound is called "aromatic." As said above we will endeavor to use only experimentally measured values of enthalpies of formation. Also, given a choice, we will consider species only in splendid isolation, in their gas phase where there are only intramolecular interactions to understand, to confound, and to help in explanations. Indeed, the term "enthalpy of formation" will refer implicitly to gas phase species unless otherwise stated. No attempt will be made to distinguish π and σ effects on stability; strain energies contributing to the latter are ignored, or more properly it is assumed that these values are independent of the number of double bonds in the ring of the heterocycle being discussed.

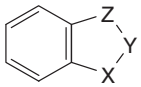
3 Indane as a Carbocyclic Paradigm

3.1 Defining Reactions

Consider the dihydroindene (indane) (**XIV**) skeleton composed of a benzene ring fused to a nonaromatic five-membered ring that lacks additional double bonds. We may consider this carbocyclic hydrocarbon with $X{=}Y{=}Z{=}CH_2$ (**XV**) as a paradigm for a



XIV



XV

XVI

variety of derivatives for which the possible aromaticity is of relevance to the current chapter. Certainly there is no reason to believe that indane will be any more aromatic than benzene or any simply alkylated derivatives thereof. Consider the formal reaction, with accompanying enthalpies of formation (kJ mol^{-1}):

$$\begin{aligned} &\text{Indane} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3(CH_2)_3CH_3 \\ &60.3 + 2(-83.8) \rightarrow 19.1 + (-146.9) \end{aligned} \tag{1}$$

This reaction is exothermic by 20.5 kJ mol^{-1}. It is not zero as might be expected since it preserves the same number and types of C−C and C−H bonds. However, a five-membered ring is destroyed in the process and its strain energy released. This reaction may be generalized to:

$$C_6H_4XYZ + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3XYZCH_3 \tag{2}$$

The endo- or exothermicity of this reaction will be taken as a probe of the aromaticity of the molecule of interest. There is an encouragingly large collection of species defined by their individual "ordered triple" of X, Y, and Z (**XV**) (e.g., if X and Y are different, then the species defined by X, Y, and Z is not the same as that defined by Y, X, and Z).

3.2 Why Not Use Monocyclic Species?

Indeed, this abundance of data is the reason why we have chosen to discuss these bicyclic species rather than the simpler, monocyclic five-membered ring compounds recognized as C_2H_2XYZ (**XVI**) for which the desired thermochemical data is very often lacking. For these monocyclic compounds we can write the related reaction:

$$C_2H_2XYZ + 2C_2H_6 \rightarrow 1,2-C_2H_2(CH_3)_2 + CH_3XYZCH_3 \tag{3}$$

The enthalpy of this reaction is the same, within a numerical constant, as the difference of enthalpies of formation of C_2H_2XYZ and CH_3XYZCH_3. Were there a more or less constant enthalpy of formation difference between methyl and phenyl derivatives (an assumption employed in [27] that "looked better" in kilocalories than in kilojoules), the enthalpy of this reaction would be the same (again to an additive constant) as the difference of the enthalpies of formation of C_2H_2XYZ and $C_6H_5XYZC_6H_5$, the defining relationship in the experimental Dewar–Breslow approach [4–6].

Most assuredly, there is a difference in strain energy of the mono and bicyclic species, as well as in phenylene (–C_6H_4–) and vinylene (–CH=CH–) bonding. However, the difference is small. Taking $C_2H_2(CH_3)_2$ as the (*Z*)-isomer of 2-butene (choosing the (*E*)-isomer introduces just an additive constant), we find the reaction:

$$\begin{aligned} &\text{Indane} + C_2H_2(CH_3)_2 \rightarrow \text{Cyclopentene} + o\text{-}C_6H_4(CH_3)_2 \\ &60.3 + (-7.1) \rightarrow 34.0 + 19.1 \end{aligned} \tag{4}$$

Deviation from thermoneutrality is by less than 1 kJ mol^{-1}, less than the error bars in the measured enthalpies of formation. This is the equivalent to the difference of reactions 1–3, equal strain energies both sides, so our previous reasoning is legitimized.

A price of our analysis is that the enthalpy of formation of some of the CH_3XYZCH_3 species will have to be estimated. In principle, one could use Benson group increments [28] in lieu of these estimates but then, many of these increments would also have to be estimated because many compounds containing the groups are unknown, inadequately precedented, or even limited to but one species, the one of interest. Benson said in a related context to one of the authors (JFL) some decades ago: "If the universe was kind, your approach would agree with mine, and both would agree with the universe."

3.3 1-Indanone and Other Keto Derivatives of Indane

3.3.1 1-Indanone

Returning now to the discussion of other carbocyclic species, we will consider the process involving 1-indanone and other keto derivatives of indane. We expect no special stabilization or destabilization over that of indane – none of these species may be expected to be aromatic or antiaromatic save that of the benzene ring therein. Starting with 1-indanone itself (X = CO, Y = Z = CH_2):

$$\begin{aligned} &\text{1-Indanone} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3(CH_2)_2COCH_3 \\ &-64.0 + 2(-83.8) \rightarrow 19.1 + (-258.8) \end{aligned} \tag{5}$$

Using the enthalpy of formation of 1-indanone from [29], we find this reaction is exothermic by 8.1 kJ mol^{-1}. We are not surprised that this reaction is less exothermic than the earlier one (1) because we have lost the conjugation energy associated with conjugation of a carbonyl group attached to a benzene ring.

3.3.2 2-Indanone

Consider now the related reaction with the isomeric 2-indanone [29] (X = Z = CH_2, Y = CO):

$$\begin{array}{l} \text{2-Indanone} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH_2COCH_2CH_3 \\ -56.6 + 2(-83.8) \rightarrow 19.1 + (-257.9) \end{array} \quad (6)$$

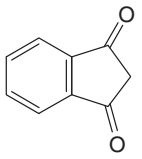
This reaction is exothermic by only 14.6 kJ mol^{-1}, in line with our expectations, since 2-indanone lacks the conjugation found in its 1-isomer. The exothermicity for 2-indanone is not the same as it is for indane. Then again, do we really expect the strain energy for 2-indanone to be the same as for indane? Are our concepts really precise to that degree of thermochemical resolution?

3.3.3 Indane-1,3-dione

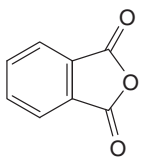
Finally, consider indane-1,3-dione [29] (X = Z = CO, Y = CH_2) (**XVII**), where we make use of the value for 2,4-pentanedione, the tautomer specified [30], and not the enol-majority mixture that is usually named this species (or even more commonly, but strictly speaking misnamed, "acetylacetone"):

$$\begin{array}{l} \text{Indane-1,3-dione} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3COCH_2COCH_3 \\ -165.0 + 2(-83.8) \rightarrow 19.1 + (-358.9) \end{array} \quad (7)$$

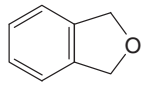
This reaction is exothermic by only 7.2 kJ mol^{-1}. Even correcting for the 1,3- or β-diketo groups, we would not expect to have twice the phenyl–carbonyl conjugation stabilization energy of 1-indanone. More precisely, there is still some destabilization because of *ortho* di-*keto* repulsions, analogous to those found in other *ortho*-disubstituted benzenes where we have electron-withdrawing substituents (e.g., CN, CN; NO_2, NO_2; NO_2, CN [31]; $COOCH_3$, $COOCH_3$ [32, 33]). So, why is indane-1,3-dione seemingly stabilized?



XVII



XVIII



XIX

3.4 Phthalic Anhydride, Phthalan and Phthalimide

3.4.1 Phthalic Anhydride

Consider now phthalic anhydride, (X = Z = CO, Y = O) (XVIII). This species has eight π electrons. Is it antiaromatic? Hückel's 4n + 2 rule would suggest this although we acknowledge that this rule strictly applies only to monocyclic species. The relevant reaction is:

$$\text{Phthalic anhydride} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3COOCOCH_3 \quad (8)$$
$$-371.4 + 2(-83.8) \rightarrow 19.1 + (-572.5)$$

This reaction is exothermic by 14.4 kJ mol^{-1}. This value is some 7 kJ mol^{-1}more exothermic than that of its carbocyclic counterpart of 1,3-indanedione. Is this to be ascribed to destabilization of phthalic anhydride and plausible antiaromaticity associated with its eight π electrons?

3.4.2 Phthalan

Before doing so, consider the corresponding reaction for phthalan (X = Z = CH_2, Y = O) (**XIX**), where no additional aromaticity is expected beyond that found in its benzene ring. Using the related reaction and the enthalpy of formation of phthalan [34]:

$$\text{Phthalan} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH_2OCH_2CH_3 \quad (9)$$
$$-30.1 + 2(-83.8) \rightarrow 19.1 + (-252.7)$$

This reaction is exothermic by 35.9 kJ mol^{-1}, some 15 kJ mol^{-1} more exothermic than indane. The reaction for phthalic anhydride is but 7 kJ mol^{-1} more exothermic than indane-1,3-dione. Putting this all together we would conclude that phthalic anhydride is stabilized relative to phthalan by 8 kJ mol^{-1}, the difference between these relative exothermicities. Is that 8 kJ mol^{-1} significant? Would we really want to say that the aromaticity of the three isomeric methylpyridines differ by 7 kJ mol^{-1}, as suggested by the spread of their enthalpies of formation? Or would we want to say that the diverse dimethylpyridines have a spread of 14 kJ mol^{-1} and hence their aromaticity varies? It is not to say that an enthalpy difference of some 7 kJ mol^{-1}, or even 14 kJ mol^{-1}, cannot significantly affect the value of an equilibrium constant or relative yields, but rather that our concepts lack resolution at that level of purported precision. Perhaps we should content ourselves with the conclusion that phthalic anhydride is mildly antiaromatic.

3.4.3 Phthalimide

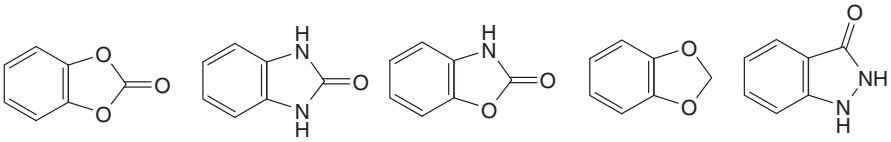
What about the nitrogen or sulfur analog of phthalic anhydride? Acknowledging earlier disparate results for solid phthalimide (X = Z = CO, Y = NH) (VIII), the enthalpy of formation of gaseous phthalimide has recently been measured as −211.1 kJ mol^{-1} [35]. Accepting this value, using the equation:

$$\text{Phthalimide} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + (CH_3CO)_2NH \quad (10)$$
$$-211.1 + 2(-83.8) \rightarrow 19.1 + (-427.6)$$

and the enthalpy of formation of acetimide [36], we found that this reaction is exothermic by 19.8 kJ mol^{-1}. While there are no enthalpy data measurements for 1,3-dihydroisoindole, the NH counterpart of phthalan, the closeness of this exothermicity to that found for phthalic anhydride makes it highly suggestive that the net degree of antiaromaticity of phthalimide is quite minimal, and somewhat more destabilizing than that found in phthalic anhydride.

3.5 Reversing Carbonyl and Ether or Amine Groups

If we reverse the carbonyl and either the ether or amine groups above, we convert the putatively antiaromatic eight-π phthalic anhydride and phthalimide into the putatively aromatic ten-π phenylene carbonate (X = Z = O, Y = CO) (XX) and 2-benzimidazolinone (X = Z = NH, Y = CO) (**XXI**), and interpolating these last species 2-benzoxazolinone (X = O, Y = CO, Z = NH) (**XXII**). Calorimetric data are absent for phenylene carbonate (benzo-1,3-dioxole-2-one).



XX XXI XXII XXIII XXIV

3.5.1 2-Benzimidazolinone

For 2-benzimidazolinone, we take the contemporary results of [37] (noting the earlier studies of solid 2-benzimidazolinone [38]) and those of [39] for *N*,*N*′-dimethylurea, for the reaction:

$$\begin{aligned} &\text{2-benzimidazolinone} + 2C_2H_6 \rightarrow \text{o-}C_6H_4(CH_3)_2 + CH_3NHCONHCH_3 \\ &-63.9 + 2(-83.8) \rightarrow 19.1 + (-224.9) \end{aligned} \quad (11)$$

This reaction is endothermic by 26 kJ mol^{-1}, very different from the exothermicities described before for the carbocycles. This strongly suggests that 2-benzimidazolone is significantly aromatic. While we lack thermochemical data for 2,3-dihydrobenzimidazole (benzimidazoline, X = Z = NH, Y = CH_2) and, for that matter, for any of its derivatives and of $CH_3NHCH_2NHCH_3$ [however, data is available for $(CH_3)_2NCH_2N(CH_3)_2$ and the polycyclic $(CH_2)_6(NH)_4$], we note that the reaction for its oxygen counterpart benzo-1,3-dioxole (X = Z = O, Y = CH_2) (**XXIII**) is exothermic by 19.4 kJ mol^{-1}:

$$\begin{aligned} &\text{Benzo-1,3-dioxole} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3OCH_2OCH_3 \\ &-142.7 + 2(-83.8) \rightarrow 19.1 + (-348.5) \end{aligned} \quad (12)$$

Benzo-1,3-dioxole (**XXIII**) is presumably nonaromatic, other than in its benzene ring. That there are ten π electrons does not make this species aromatic because the conjugation is interrupted [40, 41], much as the six-π cycloheptatriene may enjoy homoaromatic stabilization but not aromatic stabilization, per se [42]. Accordingly, we are confident that 2-benzimidazolinone (**XXI**) with its ten π electrons is aromatic.

3.5.2 2-Benzoxazolinone

For 2-benzoxazolinone (**XXII**) [37] we have the reaction:

$$\begin{aligned} &\text{2-Benzoxazolidinone} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3NHCOOCH_3 \\ &-219.0 + 2(-83.8) \rightarrow 19.1 + (-420) \end{aligned} \tag{13}$$

This reaction (13) is exothermic by 14 kJ mol^{-1} and so 2-benzoxazolinone seems to be nonaromatic. The same reaction enthalpy value as for 2-indanone (six π electrons), not far from indane (21 kJ mol^{-1}), suggests that it lacks aromaticity other than found in its benzene ring, much as found for indane and the indanones. Admittedly, the enthalpy of formation of $CH_3NHCOOCH_3$(*N*,*O*-dimethylcarbamate) is unknown; however, we may estimate the value to be –420 kJ mol^{-1} by assuming thermoneutrality for reaction 14:

$$\begin{aligned} &NH_2COOCH_3[43] + CH_3NHCONH_2[39] \rightarrow CH_3NHCOOCH_3 + NH_2CONH_2[39] \\ &-425.3 + (-231.9) \rightarrow -420 + (-237.6) \end{aligned} \tag{14}$$

3.6 Isatin and 3-Indazolinone

3.6.1 Isatin

We now turn to isatin (X = NH, Y = Z = CO) (**IX**), where we choose the contemporary measurement [44] rather than one that is a century old [45] (as cited in [46]), and to 3-indazolinone (X = Y = NH, Z = CO) (**XXIV**) (again from [37] rather than from [47]). Analysis of the energetics of the formal reactions:

$$\begin{aligned} &\text{Isatin} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3COCONHCH_3 \\ &-133.0 + 2(-83.8) \rightarrow 19.1 + (-351) \end{aligned} \tag{15}$$

$$\begin{aligned} &\text{3-Indazolinone} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CONHNHCH_3 \\ &70.2 + 2(-83.8) \rightarrow 19.1 + (-130) \end{aligned} \tag{16}$$

may appear thwarted because we lack experimentally measured enthalpy of formation data for the two acyclic amides.

However, let us make estimates. We will assume that the enthalpy of formation of $CH_3COCONHCH_3$ is the average of those of $CH_3COCOCH_3$ and $CH_3NHCOCONHCH_3$ and approximate that of the latter by assuming thermoneutrality for reaction 17:

$$\begin{aligned} &CH_3COCONH_2 + CH_3NHCONH_2[39] \rightarrow CH_3COCONHCH_3 \\ &+NH_2CONH_2[39] - 357 + (-231.9) \rightarrow -351 + (-237.6) \end{aligned} \quad (17)$$

In this reaction we have used the value −357 kJ mol^{-1} for the enthalpy of formation of $CH_3COCONH_2$. This value was estimated assuming thermoneutrality for reaction 18 and using the archival value for the enthalpy of formation of the α-diketone and that of the diamide from [48]:

$$\begin{aligned} &CH_3COCOCH_3 + NH_2COCONH_2 \rightarrow 2CH_3COCONH_2 \\ &-327.1 + (-387.1) \rightarrow 2(-357) \end{aligned} \quad (18)$$

3.6.2 3-Indazolinone

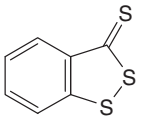
For 3-indazolinone (**XXIV**) it is necessary to estimate the enthalpy of formation of $CH_3CONHNHCH_3$. A value of −130 kJ mol^{-1} is obtained if we assume thermoneutrality for the next reaction (using a value from [49] for the enthalpy of formation of $CH_3CONHCH_3$):

$$\begin{aligned} &CH_3CONHCH_3 + CH_3NHNH_2 \rightarrow CH_3NH_2 + CH_3CONHNHCH_3 \\ &-248.0 + 94.7 \rightarrow -23.4 + (-130) \end{aligned} \quad (19)$$

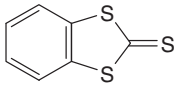
Reaction 15 for isatin is exothermic by 38 kJ mol^{-1}, thereby suggesting that isatin is significantly antiaromatic (as befits its eight π electrons). Reaction 16 for 3-indazolinone (with ten π electrons) is exothermic by 14 kJ mol^{-1}, the same value as found for 2-indanone (six π electrons) and not far from indane (21 kJ mol^{-1}). Accordingly, like 2-benzoxazolinone with ten π electrons, it is suggested to lack aromaticity other than found in its benzene ring, much as found for indane and the isomeric indanones.

3.7 Sulfur-Containing Species

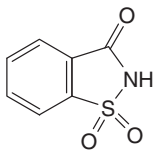
Finally, we turn to sulfur-containing species. Many indane derivatives may be suggested. However, there are only a few for which the enthalpy of formation has been determined: phenylene trithiocarbonate (benzo-1,3-dithiole-2-thione) (X = Z = S, Y = CS) (**XI**), the isomeric benzo-1,2-dithiole-3-thione (X = Y = S, Z = CS) (**X**) [50],



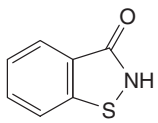
X



XI



XXV



XXVI

saccharin (X = SO_2, Y = NH, Z = CO) (**XXV**) [51], and the dideoxy derivative (**XXVI**) of the last species, (1,2-benzisothiazol-3(2H)-one) (X = S, Y = NH, Z = CO) (Matos et al. unpublished results). For the first (**XI**) we write the reaction:

$$\text{Phenylene trithiocarbonate} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3SC(S)SCH_3 \quad (20)$$
$$242.0 + 2(-83.8) \rightarrow 19.1 + 57.7$$

This reaction is essentially thermoneutral. Although we lack enthalpy of formation data for the corresponding 1,3-benzodithiole, the weakness of 1,3 sulfur–sulfur interactions as manifest by the near equality [52] of the enthalpies of formation of 1,3- and 1,4-dithiane (unlike 1,3- and 1,4-dioxane) suggests no special interaction in this nonaromatic heterocycle. Said differently, the thermoneutrality of the above reaction, as opposed to profound exothermicity (21 kJ mol^{-1}) for indane (six π electrons) and the endothermicity (29 kJ mol^{-1}) for benzimidazolinone (ten π electrons), suggests phenylene trithiocarbonate (ten π electrons) has an intermediate degree of aromaticity. For the latter two species, analysis of the related reactions:

$$\text{Benzo-1,2-dithiole-3-thione} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3C(S)SSCH_3 \quad (21)$$

$$\text{Saccharin} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3SO_2NHCOCH_3 \quad (22)$$

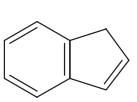
is thwarted by ignorance of the enthalpies of formation of the acyclic sulfur-containing species. More precisely, while the enthalpy of formation of a few thiolesters and dithiocarbamates are archivally known, there are no such data for "simple" dithiocarboxylates or trithio-peresters. There are also a few measurements for *N*-acylsulfonamides [53, 54] but these are for solid state species that we hesitate to use.

4 Indene as a Carbocyclic Paradigm

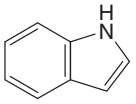
In the above we considered indane derivatives that lacked endocyclic double bonds, i.e., indene and its derivatives. However, we recall the invocation of partial double bond character between the X, Y, and/or Z groups in many of the above species. Why don't we now consider indene and its derivatives? More precisely, let us consider indene (**XXVII**) itself, with {−X−Y−} = {−CH=CH−} and Z = CH_2 and the related reaction:

$$\begin{aligned} &\text{Indene} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH_2CH = CHCH_3 \\ &163.4 + 2(-83.8) \rightarrow 19.1 + (-31.9) \end{aligned} \tag{23}$$

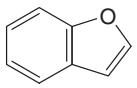
This reaction is exothermic by 8.6 kJ mol^{-1}. We are not surprised that this reaction is less exothermic than the one for indane itself because we have lost the conjugation energy associated with conjugation of the endocyclic double bond attached to a benzene ring.



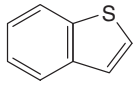
XXVII



XXVIII



XXIX



XXX

4.1 Indole, Benzo[b]furan, and Benzo[b]thiophene

Consider now indole (**XXVIII**), benzo[*b*]furan (**XXIX**) and benzo[*b*]thiophene (**XXX**) with {–X–Y–} = {–CH = CH–} and Z=–NH–, –O–, and –S– and the reactions:

$$\begin{aligned} &\text{Indole} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH = CHNHCH_3 \\ &156.6 + 2(-83.8) \rightarrow 19.1 + 40 \end{aligned} \tag{24}$$

$$\begin{aligned} &\text{Benzofuran [55]} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH = CHOCH_3 \\ &13.6 + 2(-83.8) \rightarrow 19.1 + (-134) \end{aligned} \tag{25}$$

$$\begin{aligned} &\text{Benzothiophene} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH = CHSCH_3 \\ &166.3 + 2(-83.8) \rightarrow 19.1 + 29 \end{aligned} \tag{26}$$

The enthalpy of formation of none of these 1-propenyl derivatives are known. However, they all may be reliably estimated from combining the rearrangement enthalpies:

$$CH_2 = CHCH_2ZCH_3 \rightarrow CH_3CH = CHZCH_3 \tag{27}$$

(Z = NH, −17 kJ mol^{-1} [56], Z = O, −20.2 kJ mol^{-1} [57], Z = S, (13.9 kJ mol^{-1} [58]). Estimated enthalpies of formation for the allyl species (Z = NH, 57.3; Z = O, −113.6; Z = S, 43.1) may be derived arithmetically thus:

$$\begin{aligned} &\text{Z = NH,} \\ &\tfrac{1}{2}[(CH_3CH_2CH_2)_2NH + (CH_3)_2NH] + CH_3CH = CH_2 - CH_3CH_2CH_3 \\ &\tfrac{1}{2}(-116.0 - 18.8) + 20.0 - (-104.7) = 57.3 \end{aligned} \tag{28}$$

There is no enthalpy of formation data for methyl *n*-propylamine:

$$\begin{aligned} &Z = O, \\ &CH_3CH_2CH_2OCH_3 + CH_3CH = CH_2 - CH_3CH_2CH_3 \\ &-238.1 + 20.0 - (-104.7) = -113.4 \end{aligned} \tag{29}$$

$$\begin{aligned} &\tfrac{1}{2}[(CH_3CH_2CH_2)_2O + (CH_3)_2O] + CH_3CH = CH_2 - CH_3CH_2CH_3 \\ &\tfrac{1}{2}(-293.0 - 184.1) + 20.0 - (-104.7) = -113.8 \end{aligned} \tag{30}$$

The latter expression (30), which parallels that for the Z = NH case, is seen to give an essentially indistinguishable result to the former (29), which directly uses methyl *n*-propyl ether as an input number:

$$\begin{aligned} &Z = S, \\ &CH_3CH_2CH_2SCH_3 + CH_3CH = CH_2 - CH_3CH_2CH_3 \\ &-82.2 + 20.0 - (-104.7) = 42.5 \end{aligned} \tag{31}$$

$$\begin{aligned} &\tfrac{1}{2}[(CH_3CH_2CH_2)_2S + (CH_3)_2S] + CH_3CH = CH_2 - CH_3CH_2CH_3 \\ &\tfrac{1}{2}(-125.7 - 37.4) + 20.0 - (-104.7) = 43.2 \end{aligned} \tag{32}$$

The latter expression (32), which parallels that for the Z = NH case (28), is seen to give an essentially indistinguishable result to the former (31), which directly uses methyl *n*-propyl sulfide as an input number. We may also use:

$$\begin{aligned} &CH_2 = CHCH_2SC_2H_5 + C_3H_7SCH_3 - C_3H_7SC_2H_5 \\ &21.0 - 82.2 - (-104.8) = 43.6 \end{aligned} \tag{33}$$

Indeed, all three expressions give essentially the same value for allyl methyl sulfide.

Our aromaticity-determining reactions for the three heterocycles are endothermic by 70, 40, and 48 kJ mol^{-1}, to be compared with the exothermicity for the corresponding carbocycle, indene, of nearly 9 kJ mol^{-1}. Indole, benzofuran, and benzothiophene are truly aromatic species in terms of thermochemical stabilization.

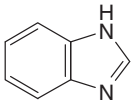
4.2 Benzimidazole, Benzoxazole, and Benzothiazole

Consider now benzimidazole (**XXXI**), benzoxazole (**XXXII**), and benzothiazole (**XXXIII**). These species are respectively {–X=Y–} = {–N=CH–}, Z = NH, O, and S, respectively, with the reactions:

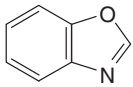
$$\text{Benzimidazole} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3N = CHNHCH_3 \quad (34)$$
$$181.7 + 2(-83.8) \rightarrow 19.1 + 28.1$$

$$\text{Benzoxazole}[59] + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3N = CHOCH_3 \quad (35)$$
$$45.1 + 2(-83.8) \rightarrow 19.1 + (-124)$$

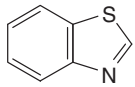
$$\text{Benzothiazole}[59] + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3N = CHSCH_3 \quad (36)$$
$$204.2 + 2(-83.8) \rightarrow 19.1 + 89$$



XXXI



XXXII



XXXIII

4.2.1 Benzimidazole

The enthalpy of formation of $CH_3N=CHNHCH_3$ is unknown and all but unprecedented. Indeed, if we exclude such cyclic and already (if only putatively) aromatic species such as adenine and cytosine, the only amidines for which the enthalpies of formation are known are 3,4,5,6-tetrahydropyrimidine [34] and the 2,4,5-triarylated imidazolines, "amarine" [60], "anisine" [60], and "hydrocinnamide" [61] from studies over a century old (as cited in [46]). The last species have only been studied as solids, and their antiquity additionally suggests ignoring these values. Accordingly, let us use the first enunciated value and assume thermoneutrality for the reaction:

$$\text{Tetrahydropyrimidine} + CH_3CH = CHCH_2CH_3 \rightarrow CH_3N = CHNHCH_3 + \text{cyclohexene} \quad (37)$$
$$55.1 + (-31.9) \rightarrow 28.1 + (-4.9)$$

We thus derive the enthalpy of formation of $CH_3N=CHNHCH_3$ to be 28.1 kJ mol^{-1} and an endothermicity of 33 kJ mol^{-1} results for benzimidazole. Benzimidazole (**XXXI**) is considerably aromatic.

4.2.2 Benzoxazole and Benzothiazole

The enthalpy of formation of $CH_3N=CHOCH_3$ also has to be estimated. Experimental measurements to derive the enthalpy of formation of imidates are as rare as they are for amidines. To do so, we assume the same enthalpy of rearrangement to the corresponding amide as measured for $CH_3N=C(CH_3)OCH_3$, 68 kJ mol^{-1} [62], and add

this to the enthalpy of formation of $HC(O)N(CH_3)_2$, −192.4 kJ mol^{-1}, to get −124 kJ mol^{-1}. So doing results in an endothermicity of 45 kJ mol^{-1} for benzoxazole, suggesting this is a significantly aromatic species. In [62] we are told that the rearrangement enthalpy for a thioamide is some 8 kJ mol^{-1} less than that of the corresponding amide. As such we take the rearrangement enthalpy to be 60 kJ mol^{-1}. The enthalpy of formation of $HC(S)N(CH_3)_2$ is unknown. Let us approximate it by assuming thermoneutrality for the reaction:

$$\begin{aligned} &HC(O)N(CH_3)_2 + C_6H_5C(S)N(CH_3)_2[63] \rightarrow \\ &HC(S)N(CH_3)_2 + C_6H_5C(O)N(CH_3)_2[64,65], \\ &-192.4 + 136.1 \rightarrow 29 + (-85) \end{aligned} \tag{38}$$

to derive 29 kJ mol^{-1} for the enthalpy of formation of $HC(S)N(CH_3)_2$ and 89 kJ mol^{-1} for $CH_3N{=}CHSCH_3$. The reactions for benzoxazole (**XXXII**) and benzothiazole (**XXXIII**) are 49 and 71 kJ mol^{-1} endothermic, suggesting considerable aromaticity for both heterocycles.

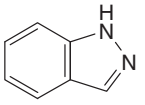
4.3 Indazole and Benzisoxazole

4.3.1 Indazole

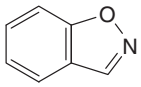
For indazole ({−X−Y−} = {−CH=N−}, Z = −NH−) (XXXIV), we naturally use the reaction:

$$\begin{aligned} &\text{Indazole} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH{=}NNHCH_3 \\ &243.0 + 2(-83.8) \rightarrow 19.1 + 138 \end{aligned} \tag{39}$$

There being no enthalpy of formation for gaseous $CH_3CH{=}NNHCH_3$, we first estimate the liquid phase value. We use the values for liquid $C_4H_9CH{=}NNHC_3H_7$ and $C_3H_7CH{=}NNHC_2H_5$, −30 and 22 kJ mol^{-1} from [66] and correct these values by five and three "universal methylene increments" of 25.7 kJ mol^{-1} [67] to result in ca. 100 kJ mol^{-1}. Estimating the enthalpy of vaporization by the CHLP protocol [68] (using three Cs, one NH as from secondary amines, and one =N− from pyridines) we derive a phase change enthalpy of 38 kJ mol^{-1}, resulting in an enthalpy of formation of gaseous $CH_3CH{=}NNHCH_3$ of 138 kJ mol^{-1}. With an endothermicity of 80 kJ mol^{-1}, indazole is suggested to have significant aromaticity.



XXXIV



XXXV

4.3.2 Benzisoxazole

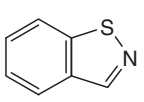
The aromaticity of benzisoxazole ({–X–Y–} = {–CH=N–}, Z = O) (XXXV) is studied using the reaction:

$$\begin{aligned} &\text{Benzisoxazole} + 2C_2H_6 \rightarrow o\text{-}C_6H_4(CH_3)_2 + CH_3CH = NOCH_3 \qquad (40)\\ &139 + 2(-83.8) \rightarrow 19.1 + (-7) \end{aligned}$$

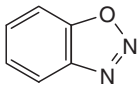
The endothermicity of this reaction is 40 kJ mol^{-1} and so we deduce benzisoxazole has significant aromaticity. No direct measurements of the enthalpy of formation of any acyclic oxime ethers appear in the literature. However, from the calculational literature [69] we find a value for the enthalpy of formation of $CH_3CH{=}NOCH_3$ of −7 kJ mol^{-1}, Unmeasured by combustion calorimetry because of experimental complications, the enthalpy of formation of benzisoxazole was recently suggested [70] to be 139 kJ mol^{-1}.

4.4 Some Additional Species

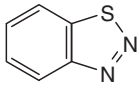
We make no comment about benzoisothiazole, ({–X–Y–} = {–CH=N–}, Z = –S–) (**XXXVI**), 1,2,3-benzoxadiazole (**XXXVII**), 1,2,3-benzothiadiazole (**XXXVIII**), or 1,2,3-benzotriazole (**XXXIX**) ({–X–Y–} = {–N=N–}, Z = –NH–,–O– and –S–) since we lack experimental measurements for the enthalpy of formation of these species in the gas phase and also for their reference species. Estimations can be made for the enthalpy of formation of all of these species, but this seems ill-advised in the current context.



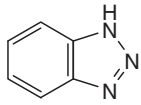
XXXVI



XXXVII



XXXVIII



XXXIX

5 Other Approaches

5.1 Another Generic Reaction for Indanes?

A plausible alternative (supplementary?) approach to the aromaticity of our diverse derivatives of indane and indene makes use of the deviation from thermoneutrality for the generic reaction:

$$C_6H_4XYZ + C_6H_6 + CH_3YCH_3 \rightarrow C_6H_5 - X - Y - CH_3 + CH_3 - Y - Z - C_6H_5 \quad (41)$$

We no longer have need of the enthalpy of formation of $CH_3–X–Y–Z–CH_3$. Again starting with the carbocyclic indane (X = Y = Z = CH_2) (XIV):

$$\begin{aligned} &\text{Indane} + C_6H_6 + CH_3CH_2CH_3 \rightarrow 2C_6H_5CH_2CH_2CH_3 \\ &60.3 + 82.6 + (-104.7) \rightarrow 2(7.9) \end{aligned} \quad (42)$$

This reaction is exothermic by 22 kJ mol^{-1}, a deviation that may be once again ascribed to release of the strain energy in the five-membered ring. (X = CO, Y = Z = CH_2):

$$\begin{aligned} &\text{1-Indanone} + C_6H_6 + CH_3CH_2CH_3 \rightarrow C_6H_5COCH_2CH_3 + C_6H_5CH_2CH_2CH_3 \\ &-64.0 + 82.6 + (-104.7) \rightarrow -100.7 + 7.9 \end{aligned} \quad (43)$$

This reaction is exothermic by 7 kJ mol^{-1}. If we argue that this is due to the strain energy of the five-membered ring, we conclude that indane and 1-indanone have different strain energies, a plausible result. For 2-indanone (X = Z = CH_2, Y = CO):

$$\begin{aligned} &\text{2-Indanone} + C_6H_6 + CH_3CH_2CH_3 \rightarrow C_6H_5COCH_2CH_3 + C_6H_5CH_2CH_2CH_3 \\ &-56.6 + 82.6 + (-104.7) \rightarrow -100.7 + 7.9 \end{aligned} \quad (44)$$

This reaction is exothermic by 14 kJ mol^{-1}, very nearly the same as for the isomeric 1-indanone. For indane-1,3-dione (X = Z = CO, Y = CH_2) (XVII) we have:

$$\begin{aligned} &\text{Indane-1,3-dione} + C_6H_6 + CH_3CH_2CH_3 \rightarrow 2C_6H_5COCH_2CH_3 \\ &-165.0 + 82.6 + (-104.7) \rightarrow 2(-100.7) \end{aligned} \quad (45)$$

This reaction is exothermic by 14 kJ mol^{-1}. We would have expected a greater exothermicity given the destabilization of the two *keto* groups. Again, we conclude there is some surprising stabilization for this diketone:

Consider now phthalic anhydride, X = Z = CO, Y = O (XVIII). This species has eight π electrons. Is it antiaromatic? Hückel's 4n + 2 rule would suggest this although we acknowledge that this rule strictly applies only to monocyclic species. The relevant reaction is:

$$\begin{aligned} &\text{Phthalic anhydride} + C_6H_6 + CH_3OCH_3 \rightarrow 2C_6H_5COOCH_3[32,33] \\ &-371.4 + 82.6 + (-184.1) \rightarrow 2(-276.1) \end{aligned} \quad (46)$$

This reaction is 79 kJ mol^{-1} exothermic. Does it follow that phthalic anhydride is significantly antiaromatic? Consider the related reaction of the unequivocally nonaromatic, acyclic acetic anhydride:

$$\begin{aligned} &CH_3C(O)OC(O)CH_3 + CH_3OCH_3 \rightarrow 2CH_3COOCH_3 \\ &-572.5 + (-184.1) \rightarrow 2(-413.3) \end{aligned} \quad (47)$$

It is exothermic by 70 kJ mol^{-1}. Anhydrides are not acyl esters or diacyl ethers, at least from the vantage point of enthalpies of formation. It was accordingly ill-advised to dismember the C(O)OC(O) group or, by inference, other XYZ groups. Our newly suggested reaction could be amended to read:

$$C_6H_4XYZ + C_6H_6 + CH_3XYCH_3 + CH_3YZCH_3 \rightarrow C_6H_5XYCH_3 + CH_3YZC_6H_5 + CH_3XYZCH_3 \quad (48)$$

However, this returns us to needing thermochemical information for CH_3XYZCH_3.

5.2 De-benzoannelation

Consider now the enthalpies of formation of our diverse indane heterocycles and corresponding one-ring species formed by de-benzoannelation (Table 1). De-benzoannelation resulting in aromatic one-ring species is generally more favorable than processes involving non- or antiaromatic species. The enthalpy of formation difference for aromatic species is typically 50–60 kJ mol^{-1}, for nonaromatic species typically ca. 30 kJ mol^{-1}, and for antiaromatic species ca. 24 kJ mol^{-1}. The difference of the enthalpies of formation between the benzoannelated and one-ring dithiol-2-thiones is −11 kJ mol^{-1}. No explanation for this discrepancy is apparent.

Table 1 Enthalpies of formation [15] of indanes and related debenzoannelated species

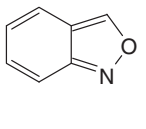
Indane/Indene	$\Delta_f H_m^0$ (kJ mol^{-1})	One-ring	$\Delta_f H_m^0$ (kJ mol^{-1})	Difference (kJ mol^{-1})
Indene	163.4	Cyclopentadiene	134.3	29
Indane	60.3	Cyclopentene	34.0	26
Phthalan	−30.1 [34]	2,5-Dihydrofuran	−67.2 [71]	37
Dihydrobenzofuran	−46.5 [55]	2,3-Dihydrofuran	−72.2 [72, 73]	26
1-Indanone	−64.0 [29]	2-Cyclopentenone	−100.3 [74]	36
Phthalic anhydride	−371.4	Maleic anhydride	−398.3	27
N-methylphthalimide	−233.9 [75][a]	*N*-methylmaleimide	−256.0 [75][a]	22
Benzofuran	13.6 [55]	Furan	−34.8	48
Benzothiophene	166.3	Thiophene	115.0	51
Benzimidazole	−181.7	Imidazole	−132.9	49
Indazole	243.0	Pyrazole	179.4	64
Indole	156.6	Pyrrole	108.4	48
Benzoxazole	45.1 [59]	Oxazole	−15.5	60
Benzisoxazole	139 [70]	Isoxazole	82.0 [34]	57
Benzothiazole	204.2 [59]	Thiazole	152[b]	52
1,3-Benzodithiole-2-thione	242.0	1,3-Dithiole-2-thione	253.0	−11

[a] We employed the data for *N*-methylphthalimide and *N*-methylmaleimide because there were no literature data for maleimide itself

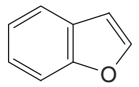
[b] This value for thiazole was obtained by assuming the same demethylation enthalpy for 4-methylthiazole as for 2-methylpyridine

5.3 What About Iso-Species?

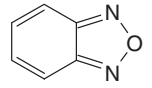
It is now admitted that all of the benzoannelated species corresponded to annelation on a formal double bond of the five-membered ring of the single-ringed heterocycles. What is to be done about the so-called iso-species? Presumably the above de-benzoannelation difference quantities can be directly compared. We know of no analog to the first procedure involving CH_3XYZCH_3 species in that these would generally be biradicals and/or zwitterions. There are few enthalpy of formation data for such species – indeed, the only cases where the heterocycle, its generally assumed less stable "iso-analog," and the one-ring species have been thermochemically investigated in the experimental literature are those of benzisoxazole (the value used above and to be used here was from solution phase studies), anthranil (**XL**) (see [70]), isoxazole [34], and isobenzofuran (**XLI**), where more precisely we are referring to the 1,3-diphenyl species for this last heterocycle [76]. There are enthalpy of formation data for benzofurazan (**XLII**) and benzofuroxan (**XLIII**) as well as for some derivatives of furazan (**XLIV**) and furoxan (**XLV**), from which the desired quantity for the parent species may



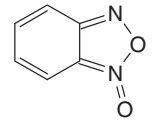
XL



XLI

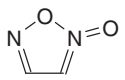


XLII

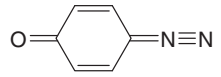


XLIII

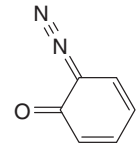
XLIV



XLV



XLVI



XLVII

be obtained. However, we have no enthalpy of formation for the isomeric 1,2,3-oxadiazole, 1,2,3-oxadiazole-*N*-oxide, or for their benzo derivatives to compare with any of these 1,3,2-species unless we allow for consideration of quinone diazides (**XLVI** and **XLVII**) [77]. (For simplicity of drawing, we show five-bonded nitrogens rather than concern ourselves with formal charges and choice of resonance structures.)

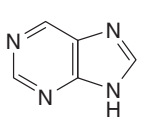
5.4 Comparison with Amides

We also note a comparison of acyclic and heterocyclic amides with the corresponding imines in which it was asserted that 3-indazolinone has considerably less

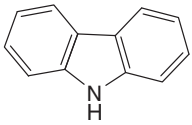
aromatic stabilization than 2-benzoxazolinone and 2-benzimidazolinone [37]. These results corroborate the conclusions from our first method discussed above.

6 More Heteroatoms and/or More Rings

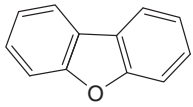
Finally, we note that all of the discussed heterocyclic derivatives of indane and indene have heteroatoms only in their five-membered ring. There are many other heterocycles related to indane that have the heteroatoms located elsewhere. However, the thermochemistry of such species is essentially uncharted. The enthalpy of formation of purine (**XLVIII**), with its four nitrogens dispersed through both rings, has been measured in recent times [78], and chronicled in the archive [15] with yet a later value [79]. These two values inexplicably differ by over 2000 kJ mol^{-1}. In the absence of a value for the enthalpy of sublimation we are hesitant to discuss this species further, other than to note two estimates from a paper more than 100 years old [80] that straddle the results in [78] by ca. ±20 kJ mol^{-1}.



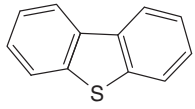
XLVIII



XLIX

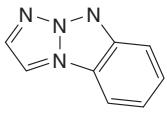


L

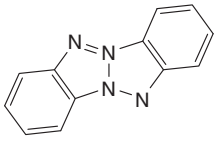


LI

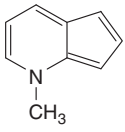
Should we wish to allow for related multi-ring species (≥ three rings), there are also enthalpy of formation data for carbazole (**XLIX**), dibenzofuran (**L**) and dibenzothiophene (**LI**), some benzo and dibenzotetraazapentalenes (also called benzoannelated triazolotriazoles) (e.g., **LII**, **LIII**, both drawn without formal charges) [81] and their nitro derivatives [82], for 4-methyl-4*H*-aza- (**LIV**) and 4-oxa-indene (**LV**) [83] (also called *N*-methyl-azalene or 1-pyrindene, and oxalene, respectively), or more properly the 2,3:5,6-dibenzo derivatives thereof, and for 1,2,4,5-benzenetetracarboxylic dianhydride (**LVI**) [84]. However, in the name of brevity we have decided not to discuss these benzoannelated species in this chapter. Instead, these await future analysis.



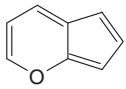
LII



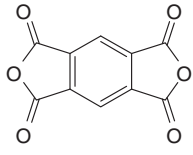
LIII



LIV



LV



LVI

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Aromatic Phosphorus Heterocycles

L. Nyulászi and Z. Benkő

Abstract Phosphorus an element with an electronegativity somewhat less than that of carbon and is an excellent and versatile building block of aromatic systems. Thus, in many systems carbon can be replaced efficiently by phosphorus. The versatility is a consequence of the many different bonding modes available for the pnicogen element. The extent of the aromaticity is different with the different bonding modes, and can also be fine tuned by utilizing various substituents that have inductive or steric effects. It is noteworthy that even small effects can have a large impact on the chemistry of these compounds. Thus, the analysis of subtle changes in aromaticity can be of importance in the future.

Keywords Aromaticity, Delocalization, Phosphorus heterocycles, Structure

Contents

Abbreviations

AIM	Atoms in molecules
ARCS	Aromatic ring current shielding
ASE	Aromatic stabilization energy

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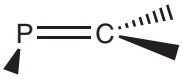
B3LYP	Becke three-parameter hybrid functional combined with Lee–Yang–Parr correlation functional
BDSHRT	Bond shortening index
BI	Bird index
CASPT2	Complete active space with second-order perturbation theory
CASSCF	Complete active space – self-consistent field method
CID	Collision-induced dissociation
DFT	Density functional theory
DME	Dimethoxyethane
ELF	Electron localization function
EPR	Electron paramagnetic resonance
GIAO	Gauge-including atomic orbital
GIMIC	Gauge-including magnetically induced current
HF	Hartree–Fock method
HOMA	Harmonic oscillator model of aromaticity
ISE	Isomeric stabilization energy
KS	Kohn–Sham (orbital)
Mes*	2,4,6-Tri-*tert*-butylphenyl (supermesityl)
NICS	Nucleus independent chemical shift
NHC	N-Heterocyclic carbenes
RE	Resonance energy
SBA	Sum of bond angles
VB	Valence bond

1 Introduction

The chemistry of phosphorus compounds has shown a steady development in the last 30 years. The most interesting results can be related to those systems having π-electrons in the broadest sense. Recent books [1–3] and review papers [4, 5] have appeared on the topic. Particularly noteworthy is the statement summarized by the title of the Mathey–Nixon–Dillon book *Phosphorus: The Carbon Copy* [2], which emphasizes the analogy between compounds of multiply bonded dicoordinate phosphorus (σ^2,λ^3-P, this notation has been used in [1]) and the unsaturated carbon (see Scheme 1).

This analogy is in fact an extension of the well established diagonal relationships (Li–Mg, Be–Al, B–Si) in the periodic table. The analogous behavior can be traced back to the similar energies of the p_z-orbitals of carbon and phosphorus as represented by the ionization energies of the CH_3 and PH_2 radicals (9.843 eV [6] and 9.824 eV [7], respectively), invoking Koopmans' theorem [8]. Not only is the ionization energy of the two radicals of similar value, but also the π ionization energies of ethene and phosphaethene are close to each other (10.51 eV [9] and 10.3 eV [10], respectively). Furthermore, in conjugated systems all the known $\pi_{C=C}$ and $\pi_{P=C}$ ioni-



Scheme 1 Double bond with σ^2,λ^3-P

zation energies have similar values exhibiting an excellent linear correlation [11]. As seen in Fig. 1 the similar energies of the occupied orbitals can be interpreted in terms of simple Hückel MO theory. For the C=C and P=C double bonds $\beta/(S + 1)$ should be of similar values, where β stands for resonance and S for the overlap parameter. Accordingly, in spite of the similar ionization energies (IE) the strength of the P=C double bond (43 kcal mol^{-1}) can be less than that of the C=C bond (65 kcal mol^{-1}), as estimated by computing the rotational barriers about the bond axis [12] or using different thermochemical cycles [12, 13]. A further important aspect from the comparison of the two double bonds is also apparent from Fig. 1. While the energies of the occupied orbitals are similar, the unoccupied orbital energies can differ (if the resonance and overlap values are smaller, the unoccupied levels are of lower values). Accordingly, the electron affinities of the systems with P=C bonds are much larger (less negative) than those of the corresponding C=C bonds [14].

It is also worth noting that the phosphorus–carbon analogy is not only restricted to the low valent phosphorus, which forms double bonded compounds. With the recent advances [15–20] in the chemistry of nucleophilic carbenes [21] it turned out that N-heterocyclic carbenes (NHC) can effectively substitute phosphine ligands in different catalysts [22], indicating the similar bonding ability of the lone pairs of tricoordinate phosphorus and (singlet) carbene. The first known NHCs, imidazole-2-ylidenes, possess six π-electrons and exhibit some aromaticity with the involvement of the empty orbital of the dicoordinate carbon [23–25]. N-heterocyclic phosphenium cations [26–28] are likewise stabilized by π-interaction from the neighboring nitrogen lone pair and exhibit a certain extent of aromaticity [29, 30]. Not only can

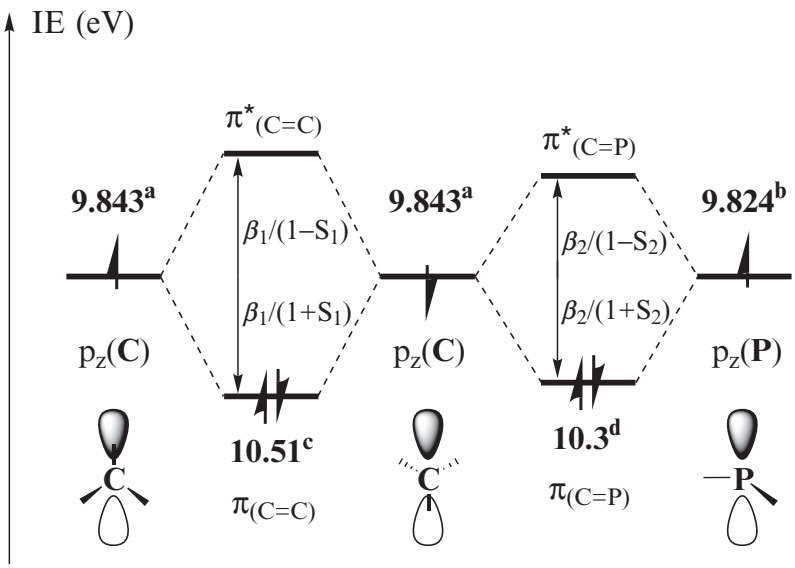


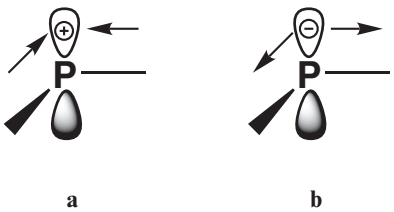
Fig. 1 Interaction between the p_z-orbitals of carbon and phosphorus, resulting in the π-systems of ethene and phosphaethene. *a,b,c,* and *d* indicate ionization energy values of CH_3, PH_2, ethene, and phosphaethene from [6], [7], [9], and [10], respectively

phosphenium cations (with their empty *p*-orbital) participate in π-systems, but also phosphide anions (being isoelectronic with sulfur) are excellent π-donor building blocks (Scheme 2). Accordingly, the cyclopentadienyl analogue phospholide (and polyphospholide) anions are known to have high aromaticity [31–33].

Phosphorus also bears a significant (positive) partial charge in neutral compounds. By expanding formally its valence shell, hypervalent bonding structures are formed, which can conveniently be described by the 3c–4e model [34, 35]. (Note that there is no need to consider the involvement of *d*-orbitals in the bonding for the hypervalent phosphorus compounds [36, 37].)

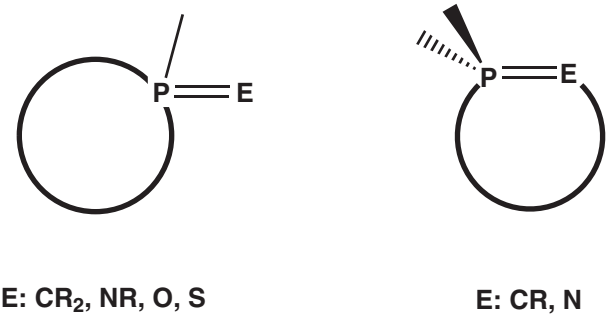
While even the saturated compounds have a significant positive partial charge at the pentacoordinate phosphorus (σ^5,λ^5-P), the unsaturated systems (with tetracoordinate phosphorus: σ^4,λ^5-P) are usually termed ylides (**IA** in Scheme 3) [38, 39] to account for the high charge separation within the molecule. Nevertheless, ylide orbitals having π-symmetry are available (ylene structure **IB** in Scheme 3) [40, 41], and the possibility for conjugation and formation of aromatic π-systems does exist [42]. The ylides can be built in a π-system with their ylidic bond (for *C*- and *N*-ylides), or by forming an exocyclic bond with the bridgehead σ^4,λ^5-P atom in the ring (Scheme 4).

The bonding in certain tricoordinate phosphorus compounds (σ^3,λ^5-P) is also termed hypervalent (**IIA** Scheme 5). In these structures the lone pair of the planar phosphorus is effectively involved in the delocalization (**IIB** Scheme 5). Bis-methylene-phosphorane (and its N, O, and S analogues) are typical examples for such bonding (Scheme 5). Like in the case of the ylides, no *d*-orbital participation is needed to describe the bonding in these compounds. Rather, the delocalized 3c–4e model can again be used [33], which also accounts for the positive charge at the central phosphorus atom, in accordance with the ylidic resonance structure (**IIC** Scheme 5).

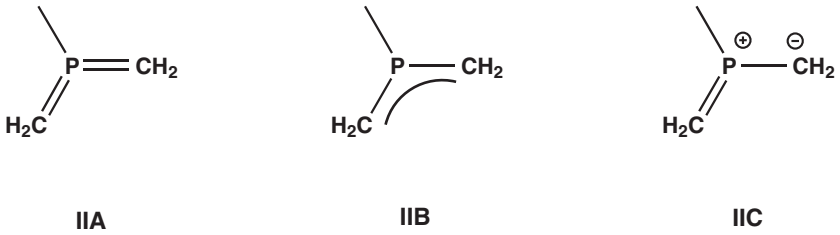


Scheme 2 Phosphenium cations (**a**) and phosphide ions (**b**)

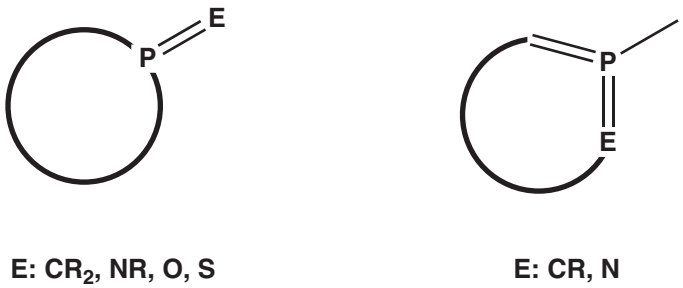
Scheme 3 Ylide and ylene bonding description with σ^4,λ^5-P



Scheme 4 Possible participation of ylides in π-systems



Scheme 5 Bis-methylene-phosphorane-type bonding with the usual notations and resonance structures



Scheme 6 Possible participation of bis-methylene-phosphorane-type bonding in π-systems

Like ylides, bis-methylene-phosphoranes can also be built into π-systems in different ways (see Scheme 6), with one of the P=E bonds in an exocyclic position, or with the entire 3c–4e π-system incorporated into the cyclic delocalization.

The lone pair of planar tricoordinate phosphorus in **II** is an excellent building block for π-systems. However, the phosphorus environment is usually strongly pyramidal (the inversion barrier in phosphine is about 35 kcal mol^{-1} [43]) and the lone pair has a considerable "*s*"-character. Accordingly, its interaction with π-systems is small. If planarized, however, the interaction becomes effective [44, 45]. It was Schleyer who first made the explicit statement: "the π-donor ability of planar tricoordinate phosphorus rivals that of nitrogen" [45]. Planarizing effects on the tricoordinate phosphorus

were summarized in detail a few years ago, and aromatic systems with planar tricoordinate phosphorus have also been discussed comprehensively [46].

Cyclic delocalized π-systems containing phosphorus with all the above discussed bonding modes can be aromatic, and their aromaticity is comparable to that of the analogous carbon compounds, as reviewed comprehensively a few years ago [4]. While the above statement needs no revision, in the last few years new compounds have been reported, and the methods used to describe the concept "aromaticity" have also been significantly refined, as shown by two recent thematical issues [47, 48] as well as a further paper [49] in *Chemical Reviews*, allowing for a more precise description of the phenomena. A further important aspect to be dealt with is related to the rapidly increasing interest in organophosphorus π-conjugated materials. While the field has recently been reviewed [50, 51], some discussion of the aromaticity aspects is of interest.

Since aromaticity is a central issue in the present report, it is of importance to summarize briefly the measures and attributes of aromaticity, while for more detailed discussion the reader is recommended recent reviews [47–49]. Although the use of quantitative measures for the description of aromaticity is questioned from time to time [52], and their direct use to rank aromaticity in different compounds might be misleading due to the multidimensional nature [53–56] of this phenomenon, the usefulness of different quantitative measures cannot be questioned. Four main criteria can be selected in the discussion of aromaticity. These are the energetic, geometric, magnetic, and reactivity criteria. Among these the latter is usually more qualitative, therefore only the first three will be mentioned briefly here.

The energetic criteria are based on the consideration that aromatic compounds are more stable than their open chain counterparts having the same number of conjugated pairs of electrons (reference compounds). The energy difference between the cyclic delocalized systems and the reference compounds is coined resonance energy (RE) [57] or aromatic stabilization energy (ASE) (for five-membered rings with one heteroatom see [58] and for its limitations for systems with more heteroatoms see [59]) or isomeric stabilization energy (ISE) (for six-membered rings see [60], and for five-membered rings see [61]). Isodesmic [62] and homodesmotic [63] reactions are often used. Their careful selection allows cancelling out of nonaromatic energetic contributions (ring strain, noncyclic conjugation, etc.). For a detailed discussion of the most proper energetic measures related to aromaticity see [59, 64]. Less commonly investigated is the effect of the stabilization on the orbital energies as represented by the ionization energies using Koopmans' theorem [8]. Stabilization (increasing) of the lone pair ionization energy values in cyclic conjugated five-membered rings with respect to the saturated counterparts becomes greater with the increasing aromaticity of these rings [65].

The geometric aromaticity criteria are related to the observations of the equalized bond length of benzene, which is in contrast with that of the conjugated polyenes, having alternating bond lengths (and bond orders). The extent of the equalization can be measured statistically, and perhaps the most widely used method is that proposed by Bird [66]. The Bird index (BI), which can also be applied for heteroatoms (including

phosphorus [67]), is determined from a projection of the standard deviations of the bond orders to a 0–100 scale. A second geometrical feature of the aromaticity is related to the stabilization, resulting in an increase of the bond orders (and consequently the shortening of the bond length). The HOMA index, which is often successfully applied, is a composite measure of this bond shortening and the bond order equalization [68]. The bond shortening (BDSHRT), which is simply obtainable as the average bond order [69], can also be used as an aromaticity indicator.

The magnetic criteria of aromaticity are related to the ring currents induced by the cyclic delocalized π-system, which perturbs the magnetic properties of the molecule. This is reflected in the measured NMR chemical shifts (e.g., in ^{1}H NMR [70–72], Li NMR [73]), or in the magnetic susceptibility (Λ) [74–76]. As for energetic measures, a key issue is to select a proper reference. The definition of the nucleus independent chemical shift (NICS) introduced by Schleyer and coworkers, which is the negative of the computed magnetic shielding at the ring center [77], has circumvented this problem and become a fashionable and simple aromaticity measure. To improve the shortcomings caused by the contribution of the σ system, computation of the dissected values NICS(π) [78] can be applied. A further (although less accurate, but computationally more simple) approach is to calculate the chemical shielding by 1 Å above the ring center NICS(1), whereby the effect of the σ contributions is reduced [78]. A further conceptual improvement is the selection of the zz components (z being the direction perpendicular to the ring plane) of the NICS tensor only ($NICS_{zz}$), as suggested by Fowler and Steiner [79], and the introduction of the $NICS_{\pi zz}$ [80, 81] where only the *zz* components from the π contributions are considered. A detailed analysis of the applicability of the different NICS indices has been published by Schleyer and coworkers [82, 83], while some concerns about using NICS as an aromaticity measure, e.g., in the case of polycylic hydrocarbons [84], have recently been published. A different (but NICS-based) approach is the investigation of the aromatic ring current shielding (ARCS), where the decay of the magnetic shielding is analyzed perpendicular to the molecular plane [85]. Investigation of the induced magnetic field has also been applied recently [86, 87].

Apart from the energetic, geometric, and magnetic measures, aromaticity is a specificity of the electronic structure. Thus, its extent can be evaluated from the analysis of the wavefunction or from that of the electron density. Among other possibilities, recent works often use the atoms in molecules (AIM) theory developed by Bader [88], which analyses the topology of the electron density within the molecule. While maxima of the electron density (characterized by negative curvature in each of the three directions) can be found at the positions of the nuclei, the path connecting pairs of chemically bound pairs of nuclei have bond critical points, with two negative and one positive curvature (the latter in the direction of the bonding path). The electron density at the bond critical point is related to the strength of the bond. The ratio of the two negative curvatures (used for the definition of a quantity called bond ellipticity) is an indicative of the symmetry of the electron density in a direction perpendicular to the bonding path, indicating the π-character of a bond. Variations of the above mentioned electron density-derived measures between related molecules indicate the extent of the electron delocalization. A further

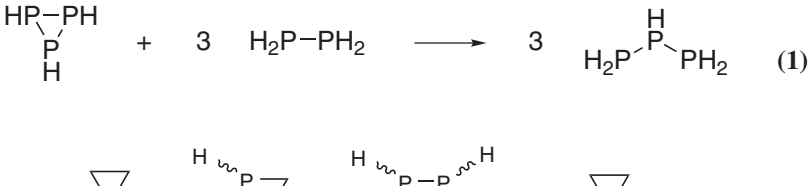
method related to the electron density is the electron localization function (ELF) [89], which can be utilized to measure the extent of aromaticity [90, 91].

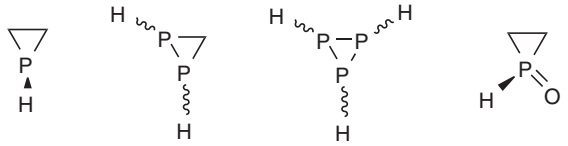
In the present paper, the aromatic (and possibly aromatic) systems will be covered and they will be organized by ring size, encompassing three-, four-, five-, and six-membered rings containing at least one phosphorus atom. When appropriate, the arsenic analogues will also be included. Since the physical phenomenon of cyclic delocalization might result either in aromaticity or in antiaromaticity these phenomena will not be treated separately. Aromaticity will be used in the broadest sense here, covering also the antiaromatic (and possibly antiaromatic) compounds.

2 Three-Membered Rings

Aromaticity is not only related to the π-system. Cyclopropane, the saturated three-membered ring is considered to be σ-aromatic [92, 93]. The σ-aromaticity, which results in stabilization [93] but also in magnetic properties [87], is not restricted to carbon. The saturated three-membered rings containing σ^3,λ^3-P atoms (**1**–**3**) (see Scheme 7) were also shown to be aromatic [94]. It is, however, difficult to separate the stabilizing effect of this type of aromaticity from ring strain.

The calculated ring strain of phosphirane (**1**, 20.2 kcal mol^{-1}) is between that of thiirane (17.3 kcal mol^{-1}) and silirane (37.1 kcal mol^{-1}) as a consequence of the differences in geminal σ-delocalization owing to the different *s* characters (and consequent narrowing of the bonding angles) of the heteroatoms. In the case of the $(H_2Si)_2E$ analogues (E: PH, S) of these rings, significant $n\rightarrow\sigma^*$ delocalization (π-delocalization) has been shown. Triphosphirane (**3**) was also reported to be σ aromatic (NICS(0) –36.7 ppm, NICS(1) –12.8 ppm, and only 26.0 kcal mol^{-1} ring strain at the B3LYP/6–311+G(3df,2p) level using the isodesmic reaction 1 [95]). Besides phosphiranes, the structure and π-aromaticity of phosphirane oxide (**4**) was also examined. Although this compound was reported to be nonaromatic [96], since only the possibility of π-aromaticity was investigated, there is no reason to believe the absence of σ-aromaticity in **4**.





1 **2** **3** **4**

Scheme 7 Saturated three-membered rings with phosphorus

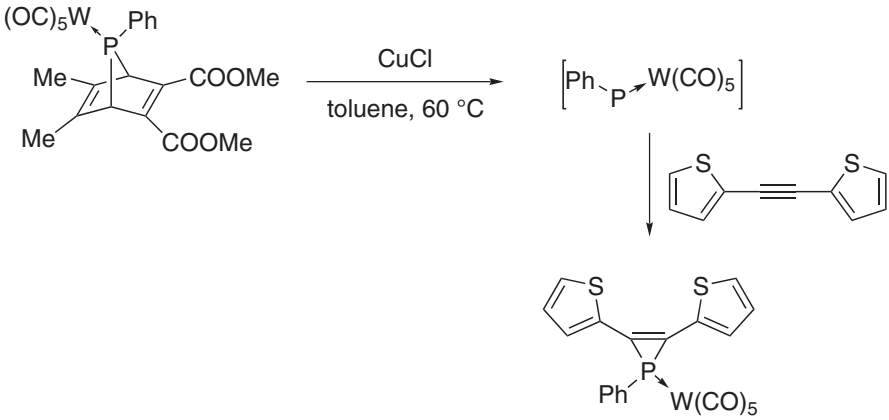
The unsaturated three-membered ring phosphirene (**5**) is nonaromatic in the π-system (similarly to cyclopropene), since the lone pair of the non-planar tricoordinate phosphorus is not available for π-interaction [96–98] (Scheme 8).

It has been stated [99] that there is no substituent effect observed in the case of 1*H*-phosphirenes (**5**). Indeed, according to the published structural data, the effect of substituents is not too large, but it varies systematically. The PC distance shortens with increasing electronegativity of the phosphorus substituent [99], in accordance with a small hyperconjugative interaction. Recently, oligomers built from (metal complexed) phosphirenes and thiophenes (see, e.g., **6** in Scheme 9) have been reported by Mathey and coworkers [100]. The products were formed from the corresponding acetylene derivatives by [2 + 1] addition of the phosphinidene complex. X-ray structural characterization has shown that the thiophene and phosphirene units are coplanar, indicating a good interring conjugation. B3LYP/6-31G* calculations indicate a good polarizability of the C=C bond in the three-membered ring, and the UV spectra of the phosphirenes exhibited a red shift with respect to the acetylene precursors, showing the effect of ring formation on the conjugation.

Unlike **5**, the phosphirene cation (**7**), in analogy to the corresponding cyclopropenylium cation [101], has been predicted [102] and shown [103] to have aromatic

5

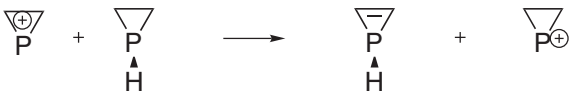
Scheme 8 Unsaturated three-membered ring phosphirene **5** and phosphirenium cation



6

Scheme 9 2,3-Dithienylphosphirene **6** reported in [100]

electron delocalization. Eisfeld and Regitz [103] have reported 32.5 kcal mol^{-1} aromatic stabilization using the isodesmic reaction 2 at the G2 level.



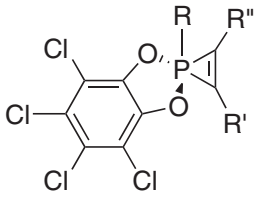
7 **(2)**

In a similar reaction at the same level for the cyclopropenylium cation, the stabilization is 59 kcal mol^{-1} [101]. Also, the equalized CC and PC bond distances are in good accordance with the aromatic behavior of the phosphirene cation. Not only does the phosphirene cation have aromatic 2π electron delocalization, but its η^3-complexed form has similar structural characteristics as well [4].

Complexed [104, 105] and uncomplexed [106] substituted phosphirene cations were observed previously in solution. Recently the parent phosphirene cation (**5**) was also generated from the reaction of PBr^+ and acetylene and characterized using mass spectrometry and high-energy collision-induced dissociation (CID) production spectra in the gas phase [107]. In the same work, the mechanism of the cation formation has been studied computationally together with other possible reactions. The phosphirene cation did not yield observable products from acetylene and ethylene (presumably because of the reversion of the product to the initial materials), but it reacted with 1,3-butadiene to afford a *P*-spiro bicyclic phosphonium ion. Besides the observed reduced reactivity of the phosphirene cation [107] as an indicative of aromaticity, the delocalization was also shown on the orbitals. Furthermore, a small (2.0 kcal mol^{-1}) destabilization was obtained in reaction 3 at the B3LYP/6-31G* level [107]. Apparently, the near thermoneutral reaction energy is attributable to the compensation of the ring strain and the aromatic stabilization.

7 **(3)**

Kawashima and coworkers have synthesized phosphiranes with pentacoordinate phosphorus (**8a**,**b**) (Scheme 10) with a stabilizing R (aryl) group at the phosphorus



8a R: Ph, R': Ph, R": Ph

8b R: Ph, R': Ph, R": $SiMe_3$

8c R: Ph, R': $SiMe_3$, R": $SiMe_3$

8d R: Cl, R': Ph, R": *t*-Bu

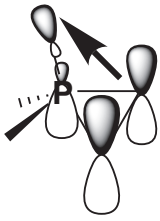
Scheme 10 Phosphirenes with pentavalent phosphorus **8a**–**8c** [108], **8d** [109]

atom [108], reacting tricoordinate phosphirenes with *o*-chloranil. This method was originally developed by Regitz and coworkers [109] for the synthesis of analogous halogeno-substituted (R: halogen) systems.

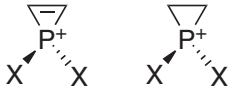
Like **8d** [109], the X-ray structure of **8a** [108] exhibited a distorted square pyramidal phosphorus. The structural parameters were similar to those obtained by DFT calculations (B3LYP/6-31G*) for **8a** and **8b**. Calculations on smaller model systems with different substituent pattern, including the tetracoordinate phosphirenium cation (see Scheme 11), allowed elucidation of the bonding, which was described by a $\pi \rightarrow \sigma^*$ delocalization [108]. This result is basically in agreement with the proposal of Regitz and coworkers [109], who used resonance structures to account for delocalization.

The structural parameters of **8** are influenced by the substituents on the carbon atoms in the three-membered ring rather than by the ligand on the phosphorus atom; silyl substitution in the computed model compounds increases the PC distance in the ring. The failure of the attempted synthesis of **8c** can be related to this destabilizing effect. Although the energetic consequence of the π–σ^* interaction in the ring was not evaluated, it was considered stabilizing since **8a** was stable for 40 h at 60 °C, in contrast with the saturated pentacoordinate phosphirane reported by Denney and coworkers [110], which decomposed at –80 °C. Also, the reactivity of the C=C double bond in the three-membered ring was lowered: the pentacoordinate phosphirenes did not undergo Diels–Alder reactions with 1,3-butadienes [108].

Like the pentacoordinate phosphirenes, tetracoordinate σ^4-phospirenium cations (**9**) (Scheme 12) show a weak hyperconjugative σ^*-aromatic stabilization [99] as the result of the interaction of the low-lying σ^*-orbital of the PX_2^+ fragment and the HC=CH fragment. This stabilization is larger for more electronegative ligands X, the fluoro derivative exhibiting significant aromaticity [4, 111]. The geometrical consequences are ligand electronegativity correlated elongations of CC bond lengths and shortenings of the CP distances, the latter being an intermediate value between that in 1*H*-phosphirenium cation **7** and the saturated analogue, the σ^4-phosphiranium cation **10**. The hyperconjugative effect in **9** is more pronounced than for 1*H*-phosphirenes (**5**) (for discussion see above).



Scheme 11 $\pi \rightarrow \sigma^*$ interaction in pentacoordinate phosphirenes **8**



Scheme 12 σ^4-Phospirenium cation **9** and σ^4-phospiranium cation **10** **9** **10**

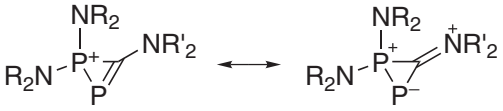
Although neither phosphirane oxide (**4**) nor 1*H*-phosphirene (**5**) are aromatic species, the phosphirene oxide **11** (and its arsenic analogue) possesses enhanced aromatic characteristics. This behavior was explained by the electron-withdrawing effect of the oxygen, which is easily understandable considering the ylidic structure of the phosphorus–oxygen bond (Scheme 13). For this compound, 17.9 kcal mol^{-1} stabilization was obtained (for arsirene oxide 14.5 kcal mol^{-1}) in the isodesmic reaction 4. In contrast, 3.2 kcal mol^{-1} destabilization was reported for azirine oxide, which was attributed to the high electronegativity of nitrogen, disfavoring the charge separation. Furthermore, from geometrical parameters, calculated chemical shifts, AIM analyses, and from the topology of the electron localization function (ELF) it was concluded that the oxides of phosphirene and arsirene are aromatic molecules.

(4)

The structurally characterized derivative of the diphosphirenium cation **12** is a known species [112–116]. The gas-phase synthesis and pentaquadrupole MS characterization, and CID (with argon) of the first azaphosphirenium cation **13** (the N,P analogue of the cyclopropenyl cation) were also reported recently [117] (Scheme 14). Although this compound has not been characterized structurally, the similarity of the B3LYP/6-311++G** calculated PC and CN(exocyclic) bond lengths of **13** to

11a **11b**

Scheme 13 Phosphirene-oxide **11**, with ylenic (**11a**) and ylidic (**11b**) description of the PO bond



12a **12b**

R,R': *i*-Pr

13a **13b**

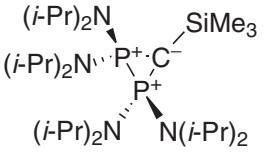
R,R': Me

Scheme 14 The diphospirenium **12** [116] and azaphosphirenium **13** [117] cations

the corresponding X-ray-determined bond lengths of its diphosphorus analogue **12** [116] was found remarkable.

The stability of these cations is enhanced by the amino substituent, which is also known to increase considerably the stability of the cyclopropenyl cation [118]. The 1.69 and 1.74 Å PC bond length of **13** (calculated) and **12** (measured), respectively [118], are clearly longer than the 1.63 Å value of the neutral 2*H*-phosphirene [119], whereas the CN bond length is clearly in the CN double-bond range. Thus, for description of the bonding in **12** and **13** the **b**-type mesomeric structure was preferred [118].

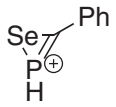
The diphosphirenium cation with two σ^4,λ^5-P atoms (**14**) has also been reported. For an explanation of its stability, the effect of σ* aromaticity (interaction of the lone pair at the carbanion with the σ^*_{PN} antibonding orbitals) has been considered, although it has not been further investigated [120].



14

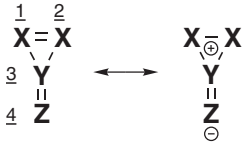
The presence of the apparently delocalized selenaphospirenium cation **15** has also been observed as a reaction intermediate by ^{31}P NMR spectroscopy with the non-coordinating counteranion $CF_3SO_3^-$; however, the extent of its aromaticity has not been investigated [121] (Scheme 15).

The aromatic character of mono-, di-, tri-, and tetraphosphatriafulvenes has recently been calculated [122, 123] using DFT methods (Scheme 16). The energy of the donor–acceptor interaction between the Lewis-type π-orbital of the ring and the antibonding π*-orbital of the *exo*-bond was computed by second-order



15

Scheme 15 The selenaphospirenium **15** [121] cation observed as intermediate by ^{31}P NMR



16a **16b**

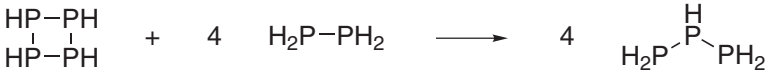
Scheme 16 Phosphatriafulvenes X=CH,P Y=C,P Z=CH_2,PH,P

perturbation theory, and this can be used to measure the aromaticity of triafulvenes.

Based on this analysis, not only the electronegativity of the substituent atoms, but also the lengths of the bonds are related to the aromaticity of triafulvenes. The aromaticity is reported to decrease if the ring-carbons are substituted by phosphorus [123]. The aromatic stabilization effect of the *exo*-phosphorus is greater than the destabilization effect of the ring-phosphorus atom. 3,4-Diphosphatriafulvene and 1,2,3,4-tetraphosphatriafulvene were found to be ylides with negligible aromatic character. The order of the aromaticity is as follows: cyclopropenone > 4-silatriafulvene ≈ 4-phosphatriafulvene > 1,4-diphosphatriafulvene > methylenecyclopropene > 1-phosphatriafulvene > 1,2,4-triphosphatriafulvene > 1,2-diphosphatriafulvene > 3,4-diphosphatriafulvene > 1,2,3,4-tetraphosphatriafulvene [123].

3 Four-Membered Rings

Saturated four-membered rings are suggested to have antiaromatic character on the basis of their (positive) NICS properties, in accordance with the $4n + 2/4n$ rule [124]. This has been proven for rings with σ^3,λ^3-P atoms as reported by Schleyer and coworkers [95]. For the saturated ring tetraphosphetane $(PH)_4$, positive NICS values (NICS(0) 8.5, NICS(1) 8.6 ppm), were obtained. The strain energy obtained from reaction 5 was somewhat larger (32.8 kcal mol^{-1}) than the 26 kcal mol^{-1} for three-membered rings (reaction 1), in spite of the expected alleviation of the ring strain with the 90° bonding angle, which should be favorable for phosphorus.



(5)

Like cyclobutadiene, its σ^2,λ^3-P analogues obtained by replacement of the CH units in the ring by phosphorus (**16**–**20**) are highly antiaromatic compounds (Scheme 17). Perhaps the best demonstration of the destabilization in this four-membered planar ring system is that this form of P_4 (**20**) has never been observed, while the tetrahedral form (white phosphorus), which was shown to be aromatic [124], is well known. The antiaromaticity has been discussed before for the rectangular 1,3-diphosphacyclobutadiene [4]. It exhibited 40 kcal mol^{-1} destabilization with respect to the open chain diphosphabutadiene reference, of which about 10 kcal mol^{-1} was attributed to ring strain [125].

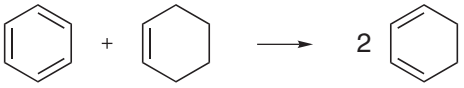
17 **18a** **18b** **19** **20** **21**

Scheme 17 Four-membered unsaturated rings with different numbers of σ^2,λ^3-P atoms

Wang and Schleyer [126] have investigated the aromaticity of **17**, obtaining highly positive NICS values (NICS(0) +30.7, NICS(1) +19.6 ppm), as indicatives of significant antiaromaticity. In a recent study, all the possible $C_2P_2H_2$ isomers were investigated [122]. It is noteworthy that 1,2-diphosphete (**18**) exhibits two bond stretch isomers, of which **18b** is more stable than **18a** by 19.2 kJ mol^{-1} (4.6 kcal mol^{-1}, CASPT2/ANO-L//CASSCF(21,11)/ANO-L) ("Method1//Method2" description means that the property was calculated at the "Method1" level at a geometry calculated at the "Method2" level of theory). The +36.2 ppm NICS(0) value for **19** [122] also indicates a significant antiaromaticity.

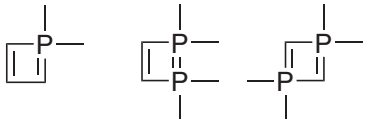
The (anti)aromaticity of four-membered ring heterocycles containing one or more P atoms (including **17**–**20**) has been discussed in a recent review paper [127]. Using a difference of hydrogenation reaction energies between partially and fully saturated rings (in fact this is an isodesmic reaction, illustrated in the cases of cyclobutadiene and benzene as reactions 6 and 7, respectively) a linear aromaticity scale (in %) has been created. As the two extremes, the destabilization energy of cyclobutadiene and the stabilization energy of benzene span the –100% to +100% range [128]. As discussed by Mucsi and Csizmadia in their review [127], the "aromaticity%" values of **17**, **19**, **20**, and **21** were –79%, –69%, –56%, and –70%, respectively, all indicating significant antiaromaticity in accordance with the results obtained from the other investigations. The similar aromaticity of these compounds provides a further example for the phosphorus–carbon analogy in their unsaturated compounds. It is in accordance with these results that neither **17**–**21** nor their C-substituted derivatives has been observed so far. It is interesting to note that the *tert*-butyl derivative of **19**, as a suspected reaction intermediate obtainable from *t*-BuCP as a dimerization product in many cycloaddition reactions, was extensively investigated by the Regitz group, but without success (Regitz M., personal communication).

(6)



(7)

Among the σ^4,λ^5-P analogues of **17**–**21**, only **22**–**24** (Scheme 18) are of practical importance, since it is hard to accommodate the increasing number of positively charged σ^4,λ^5-P atoms in the four-membered ring. The aromaticity% values [128], discussed by Mucsi and Csizmadia [127], are –8%, +46%, and –46% for **22**, **23**, and **24**, respectively. All these values indicate significantly less destabilization than



22 **23** **24**

Scheme 18 Four-membered unsaturated rings **22**–**24** with one and two σ^4,λ^5-P atoms

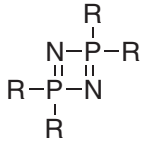
in their σ^2,λ^3-P analogues, with the exception of **24**. In the case of **22**, 1.6 ppm was reported for NICS(0) in agreement with the small antiaromaticity concluded from the aromaticity%. Replacement of the hydrogens on phosphorus by fluorine changed the NICS(0) to 0.6 ppm [126], indicating nonaromaticity. This substituent effect on phosphorus is small; however, it is in accordance with the previously noted influence of fluoro substitution in the case of σ^4-phosphirenium cations [99, 111]. In contrast, the aromaticity% [128] indicates that upon fluorination the antiaromaticity shows some increase (to –20%) [127]. The stabilization of four-membered rings with (at least) one σ^4,λ^5-P atom has been noted before [129], and the bonding structure was described either as a delocalized ylide [129], or as a one-way delocalized structure [125] formed with an allyl-like π-system.

The reported +46% aromaticity% (i.e., stabilization) [128] for **23** is somewhat surprising. Previously it has been reported [130] that the parent compound (with hydrogens on P and C) cannot be optimized as a four-membered ring, opening up at the PP bond, while it could be stabilized by amino (at P) and silyl (at C) substitution, in accordance with the substituent pattern of synthesized derivatives of **23** [129].

The destabilization of **24** as indicated by the -46% aromaticity% [127] is in disagreement with the earlier results [125], where open chain reference compounds were used, and after correction to the ring strain some stabilization was obtained. It is somewhat unfortunate that in the review [127] all the calculated aromaticity% data are given without the energy values of the hydrogenation reactions used, which makes the interpretation of these results difficult. Nevertheless, the fact that several substituted derivatives of **24** (for a recent example see [130]) could have been synthesized indicates the stability of the ring system (which is obviously further enhanced by the applied substituents). Further support for the aromaticity of the 1,3-σ^4,λ^5-P-1,3-diphosphete ring system (**24**) comes from a recent investigation of the derivative of the analogous four-membered fluorocyclophosphazene ring **25** (R: F, see Scheme 19), exhibiting a -10.9 NICS value (B3LYP/6-311++G) [131].

λ^5-Heterophosphetes with additional (apart from the σ^4,λ^5-P) heteroatoms such as N or σ^2,λ^3-P; σ^3,λ^5-P; and σ^4,λ^5-P (**23**) and are known [129]. In the case of σ^4,λ^5-P,σ^2,λ^3-P-1,2-diphosphete, the delocalization in the ring has been investigated and the stabilizing effect of the amino and silyl substituents used has been established [132] by using isodesmic ring fragmentation reactions. The electronic structure in this ring was similar to that in **22**.

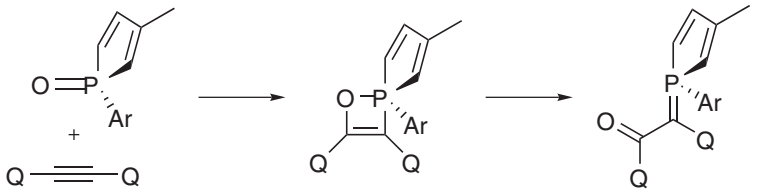
A further four-membered ring system is the heterophosphete family **26** shown in Scheme 20, with E:O, NH, S. The saturated analogue of the ring (in the case of E: O) is the intermediate of the Wittig reaction [133]. **26** (E:O) itself was found com-



Scheme 19 1,3-Diaza,2,4σ^4,λ^5-P-diphosphete (**25**) **25**

26a **26b**

Scheme 20 Four-membered unsaturated rings **26** with E: O, NH, and S and one σ^5,λ^5-P atom



26O
Q: COOR

Scheme 21 Inverse Wittig-reaction with the intermediate four-membered ring **26O**

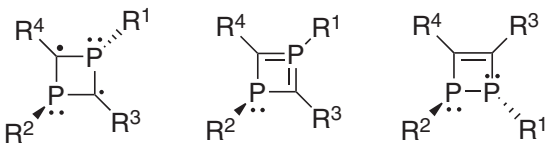
putationally as a high energy structure on the inverse-Wittig reaction path [134] and reviewed [135] by Keglevich and coworkers (Scheme 21). **26** with E: N [136] was characterized by X-ray crystallography (however, with a PN distance somewhat longer than 2 Å), and **26** E:S [137] was also characterized spectroscopically. The observability of these compounds is apparently attributable to the presence of the stabilizing Martin-ligand attached to the pentavalent phosphorus.

Considering that the instability of **26** is due to its antiaromatic character, Mucsi et al. [138] computed the structure of **26** (E:O, N, S), and have established that with X:F, Cl, or CN (all electronegative groups) a stable minimum can be obtained. The **26a** structures exhibited negative aromaticity% [128] of between –10% and –40%, while the **26b** structures have shown values of about –10% and +10%, indicating comparatively less destabilization. The antiaromaticity has been explained by the participation of the phosphorus *d*-orbitals in the bonding. The effect of the *d*-orbitals was attributed to the increased antiaromaticity (negative shift of the aromaticity% value [128]), and to the shortening of some bond lengths (e.g., PO) by adding *d* functions to the basis set [138]. It should be noted that the authors themselves noted that the *d*-orbitals of phosphorus have small coefficients in the occupied MOs, which are comparable to the coefficients of the *d*-orbitals used as polarization functions on the lighter elements [138]. Thus it is likely that, in accordance with previous analysis of the bonding in hypervalent compounds [36, 37], the *d*-orbitals do not play a significant role in the antiaromatic structure but act mainly as polarization functions, making the basis set more flexible. The observed geometric changes and antiaromatic character can be explained by considering interactions with the hyperconjugative σ-orbitals, as for the hypervalent σ^4-phosphirenium cations [99, 111] discussed above.

Among four-membered rings with two σ^3-P atoms, biradicaloid structures are known. The first example of these compounds **27** (R^1: Mes*, R^2:Mes*, R^3:Cl, R^4:Cl) synthesized by the Niecke group [139] was based on the 1,3-diphosphete-2,4-diyl ring (Scheme 22). The computationally studied optimized structure of the parent compound **27** (R^1:H, R^2:H, R^3:H, R^4:H) has two pyramidal phosphorus atoms and, having formally two unpaired electrons (see **27A** in Scheme 22), was shown to be less stable by 247 kJ mol^{-1} (59.1 kcal mol^{-1}) at the MCSCF(10,10)/6-31G* level than its isomer **28** [140]. Although the parent **27** has a singlet ground state, the triplet is only slightly (by 6 kcal mol^{-1}) less stable [141], in agreement with the supposed biradicaloid character (**27A** Scheme 22). This structure has apparently little aromaticity, while the computed structure with both phosphorus planarized (a second-order saddle point) [139] exhibited significant aromaticity with 6π electrons, as shown by the exaltation of the magnetic susceptibility [4]. Substituent effects, however, can increase the singlet–triplet gap [140], which is supposedly related to the delocalization of the odd electrons, stabilizing the singlet. The bulky Mes* groups at phosphorus are apparently planarizing, as seen from the bond angle sum (about 340°) obtained from the published X-ray structure of **27** (R^1:Mes*, R^2:Mes*, R^3:Cl, R^4:Cl) [139] and **27** (R^1:Mes*, R^2:Mes*, R^3:H, R^4:$SiMe_3$) [142], allowing for some aromatic delocalization in the ring, the extent of which remains to be explored. A further hint for the delocalization comes from the PC bond lengths, which vary between 1.72 and 1.73 Å in **27** (R^1:Mes*, R^2:Mes*, R^3:H, R^4:$SiMe_3$) [141], a value that is considerably shorter than the PC single bond (that should be about 1.8 Å).

It is interesting to note that the inversion barrier at a single phosphorus atom only is small in **27**, as shown for the parent system **27** (R^1:H, R^2:H, R^3:H, R^4:H) [139], resulting in a first-order saddle point. Having substituents with different steric bulk at the two phosphorus atoms, as in the case of the derivative (R^1:*t*-Bu, R^2:Me, R^3: Mes*, R^4:Mes*) synthesized by Yoshifuji and coworkers [143], the phosphorus with the small methyl group becomes more pyramidal (SBA: 319°), with simultaneous lengthening of the ring $CP^{(pyramidal)}$ bonds according to the X-ray structural analysis. These structural characteristics resemble more **27B**, having apparently less extended cyclic conjugation than the **27A** form.

The electron-rich **27** is very reactive. **27** (R^1:Mes*, R^2:Mes*, R^3:H, R^4:$SiMe_3$) furnishes an anionic carbene upon deprotonation [144]. This compound forms an



27A **27B** **28**

Scheme 22 Two possible bonding structures to describe 1,3-diphosphete-2,4-diyl (**27**) and its double bonded isomer 1,2-diphosphete (**28**)

alane complex, and has rather flattened phosphorus atoms with a bond angle sum of about 340° [144] as an indicative of its 6π-electron structure. Reaction of **27** (R^1: Mes*, R^2:Mes*, R^3:$SiMe_3$, R^4:$SiMe_3$) with Li or K in DME cleaves the PC(aryl) bonds resulting in the dianion **29**, which was characterized by its X-ray crystallographically as a bis-η^4-Li^+ DME complexed structure. The reaction path was explored by B3LYP/6-31+G* calculations [145] and the computed structure of the product **29** is shown in Fig. 2. The aromaticity of the dianion is shown by the equalized PC bond lengths and by the –7 ppm NICS(0) value obtained at the B3LYP/6-311+G**//B3LYP/6-31+G* level. Also, the –4.6 ppm δ^7-Li shielding indicates a diatropic ring current [145]. It is worth noting that a cyclobutadienediide $(CSiMe_3)_4^{2-}$, the all-carbon analogue of **29**, has been reported as well as a bis-η^4-Li^+ DME capped complex **30** [146, 147], exhibiting similar characteristics (if comparable) to **29**. Also, the NICS value calculated for **30** [145] was –9.2 ppm, a value that is somewhat larger than that for the phosphorus analogue **29**, giving a further example of the similarity of unsaturated phosphorus and carbon compounds. The aromaticity of Li^+ capped cyclobutanediide has also been studied by Schleyer and coworkers [148], who reported more negative (aromatic) NICS values. The difference can probably be attributed to the alkyl substituents, which were attached to the four-membered ring instead of the $SiMe_3$ groups [148].

Not only have the caclobutadienediide and its diphospha analogue been synthesized recently but also an interesting example of the dianionic structure derived from

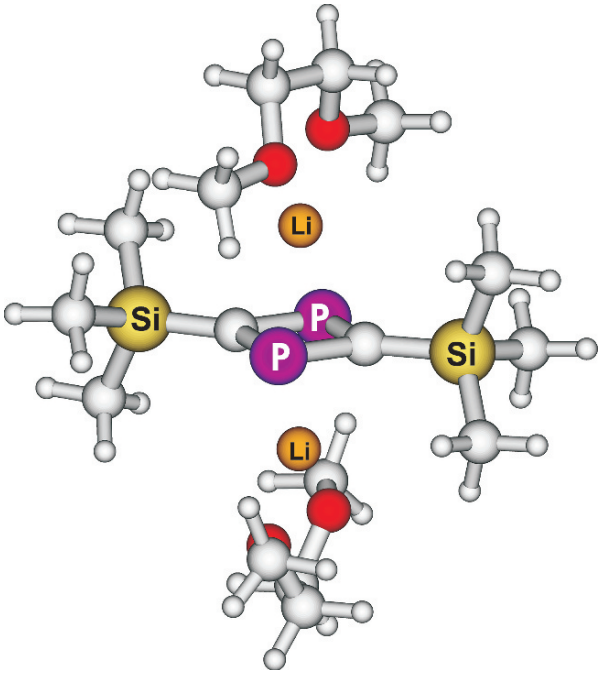
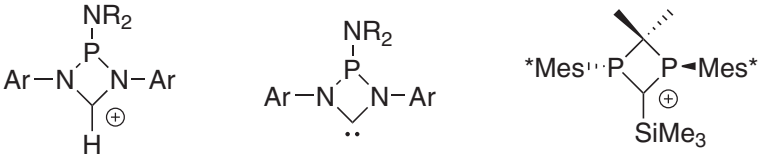


Fig. 2 B3LYP/6-31+G* optimized structure of dianion **29**, complexed with two Li^+ DME

planar P_4 has been reported by Korber and coworkers as $Cs_2P_4.2(NH_3)$ [149] and $(M@18\text{-crown-6})_2P_4$ [150], following the synthesis of the arsenic analogue [151]. Also, the photoelectron spectrum of the NaP_4^- anion has been measured, and evaluated by ab initio calculations [152]. The aromaticity of P_4^{2-} has been studied by investigating the ELF [153]. It has been established that there is a comparable variance and population of the disynaptic valence basins of P_4^{2-} and P_5^-, the latter being highly aromatic. However, both values are smaller than for benzene, while the analysis of the monosynaptic basins indicated that the lone pairs contribute significantly to aromaticity in these compounds. The effect has been termed lone pair aromaticity [152]. The aromaticity of M_2P_4 (M: Li, Na, K) and MP_4 (M: Be, Mg, Ca) complexes has also been studied [153]. It has been found that the square planar P_4 structural motif shows little variance in this series of compounds. Furthermore, the Wiberg bond indices are between the single and double bond values and the MOs are characteristic for an aromatic system [154]. Structures and NICS values for the first row transition metal complexes for P_4 as $P_4MP_4^{n-}$ have also been studied very recently [155]. Ti, V, Cr, and Mn species exhibit σ and π antiaromaticity, while the Fe, Co, and Ni show σ and π aromaticity [155].

Observation of the dianions of the four-membered phosphorus-containing rings raises the question of whether the previously observed complexes of **17**–**20**, which have planar four-membered rings with equalized bond lengths, are in fact dianions complexed by the cationic form of the transition metal. Furthermore, cage compounds formed from main group elements (Ge [156], Sn [157], and P^+ [158]) and 1,3-diphosphete can also be described as complexed dianions. Mucsi and Csizmadia have studied these complexes in their recent review [127]. In each case they have obtained an aromaticity% value [128] of 40–70%, indicating significant aromatic stabilization. While they attributed the aromaticity to the formation of a dicationic system in the four-membered ring (2π electrons) in each case [127], the description of these complexes with the dianionic form (which has not been considered) is a possibility that remains to be investigated.

A cationic species with phosphorus in a four-membered ring with a π-delocalized system is provided by the 1,3-diaza-2-phosphetin system. Majoral and coworkers [159] first reported such a ring, and more recently Despagnet-Ayoub and Grubbs [160] presented an X-ray structure of **31** (R:*i*-Pr, Ar:Mes, 2,6-diisopropylphenyl, Scheme 23) with the non-coordinating triflate anion. However, the rather



31 **32** **33**

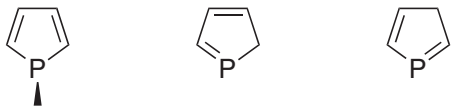
Scheme 23 1,3-Diaza-2-phosphetine (**31**), and the corresponding stable carbene 1,3-diaza-2-phosphetine-4-ylidene (**32**) and the bis-phosphanylcarbenium ion **33**

short exocyclic 1.622 Å PN distance (as compared to the 1.824 Å value for the inter-ring distance) indicates that the π-conjugation is extended on the NCN fragment only. Treatment of **31** (R:*i*-Pr, Ar:2,6-diisopropylphenyl) resulted in the stable carbene **32**, which has also been characterized structurally and exhibits similar features to **31** [160]. An interesting four-membered cationic ring with strong π-delocalization, despite the pyramidality of the two σ^3,λ^3-P atoms, is exhibited by **33**. The delocalization stabilization estimated by an isodesmic reaction was 130 kcal mol^{-1}, explained by the interaction between the empty orbital of the cationic center and the antibonding combination of the two *s*-type lone pairs of the pyramidal phosphorus centers. Although this ring is nonaromatic because of the presence of the saturated carbon, the delocalized P–C(+)–P unit can serve as a building block for cyclic delocalized systems [161].

4 Five-Membered Rings

Five-membered rings with at least one phosphorus atom and two double bonds are termed phospholes. The parent molecule can exist as 1*H*-phosphole **34**, 2*H*-phosphole **35**, and 3*H*-phosphole **36** (Scheme 24). **35** and **36** are apparently nonaromatic, as is cyclopentadiene [162]. Interestingly, however, the parent **35** is more stable than **34** [163, 164], while **36** is the least stable isomer, as recently discussed comprehensively by Mathey [165]. Due to its cyclopentadiene-type reactivity, **35** is usually a transient species; however, it can be complexed and therefore its hitherto largely unexplored chemistry is even more promising than that of cyclopentadiene [164].

Following some initial controversial assumptions, the extent of aromaticity in **34** is now clearly established [1–5, 165]. Phosphole is non-planar, and thus the heteroatom lone pair (with large *s* character) is unavailable for π-conjugation due to symmetry reasons. The non-planarity is understandable considering that the inversion barrier of the tricoordinate phosphorus (plus the ring strain, which increases upon planarization [46]) is larger than the aromatic stabilization energy gained upon interaction with the *p*-type lone pair of the planar phosphorus. This was first suggested by Mislow, who noted the lower (by ca. 20 kcal mol^{-1}) inversion barrier of a phosphole derivative as compared to that in the saturated (phospholane) ring [166]. Although the lone pair is not available for cyclic conjugation, the different aromaticity measures of phosphole are slightly larger than for cyclopentadiene (with the exception of HOMA), as summarized in Table 1.



34 **35** **36**

Scheme 24 1*H*-Phosphole (**34**), 2*H*-phosphole (**35**), and 3*H*-phosphole (**36**)

Table 1 Collected aromaticity measures for cyclopentadiene and phosphole (**34**)

	Cyclopentadiene	Phosphole
HOMA	0.306 [64]	0.236 [64]
Bird index	29 [162]	46 [33]
BDSHRT	45 [162]	50 [33]
ASE [see (8)][a]	2.6 [33]	5.8 [33]
ISE_c [see (9)]	0.0 [61]	2.6 [61]
NICS(0)	–3.1 [162]	–5.0 [33]
NICS(1)	–4.8 [64]	–6.0 [64]
ΔΛ	–2.4 [33]	–5.3 [33]

All the data from the literature were reported at B3LYP/6-311+G**. ASE[a] and ISE are given in kcal mol^{-1}; NICS(0) and NICS(1) in ppm. ΔΛ is the exaltation of the magnetic susceptibility
[a]In the case of having a single heteroatom, reaction 8 is properly balanced. For details see [59, 64]

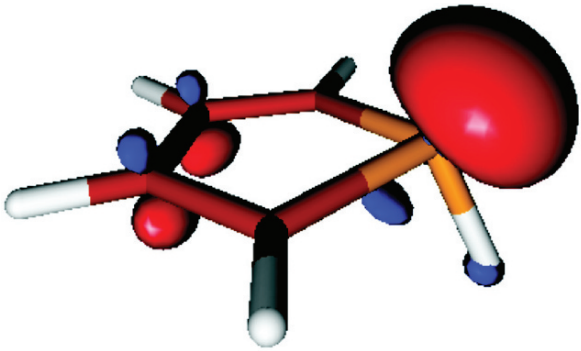
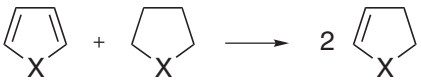
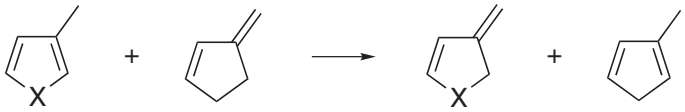


Fig. 3 The B3LYP/6-31G* HOMO-1 KS orbital of phosphole, which is mainly localized at the phosphorus, having small π and σ_{PH} contributions



(8)



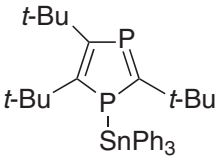
(9)

The small stabilization is attributable to hyperconjugation with the σ- and σ*-orbitals formed between the phosphorus and its substituent, and is therefore of hyperconjugative nature. This was recognized from early photoelectron spectroscopic investigations [167], but since the extent of the effect is small, the literature mainly contains cautious statements about its nature. The interaction between the π-system, the s_{PH}-orbitals, and the phosphorus lone pair can clearly be seen in Fig. 3.

More importantly, it has been noted that some electronegative substituents (which increase the negative hyperconjugation) at P increase the dienic reactivity of phosphole [168]. This chemical behavior is related to a decrease of the aromaticity, and the effect could also be detected in variations of the aromaticity indices such as NICS, ASE, and BI [169]. Nevertheless, the effects are small (e.g., for NICS(0) the largest negative value was exhibited by phosphole itself and was -5.0, while the smallest value for 1*F*-phosphole was –0.9 ppm). These small variations, however, did not correlate with the pyramidalization of phosphorus, which, if reduced, has a much larger effect on aromaticity. While the hyperconjugative interaction with electronegative elements decreases the aromaticity (the reduced aromaticity of 1-fluorophosphole has also been noted in investigations of some isodesmic reactions, including ASE, by Chesnut [170]), the electropositive stannyl group had no effect on the aromaticity of 1,3-diphoshole as shown by NICS(0) and BI [171]. Apparently the interplay between the interactions of the π-system with the hyperconjugative orbital (as shown on the MOs) and with the lone pair of the somewhat flattened phosphorus of the diphosphole [33] results is no net change in the aromaticity. The 1-stannyl-1,3-diphosphole **37** (Scheme 25) has shown a fluxional behavior, for the movement of the stannyl group with low barriers about the diphosphole is a circumambulatory motion [171]. Similar behavior ("windscreen motion") was observed for the 1-stannyl-1,2,4-triphosphole **38** (Scheme 25) investigated in detail by Zenneck and coworkers [172].

Other metal substituents such as Hg [173] further decrease the barrier, and in the case of Cu both η^1- and η^5-complexation of the triphosphole could be observed [174]. Apparently the low barrier is related to the stability of the transition structure, whereby the ring is highly anionic and exhibits aromaticity [5] (see also below).

The effect of negative hyperconjugation is even more extended in the case of phospholes with hypervalent σ^4,λ^5-P (with the substituent bound in an exocyclic fashion), such as the phosphole oxides. These compounds are known to be unstable, dimerizing easily in a [4 + 2] fashion [175]. This observation can be related to some destabilization of the π-system in the ring, as in the case of phosphole itself. The unexpected isomerization of a phosphole derivative **39** (shown in Scheme 26) could also be interpreted by considering the destabilization in the corresponding phosphole sulfide (**39 = S**), which rearranges to **40** in order to escape from the unfavorable electronic situation [61]. The aromaticity indices were calculated for hypervalent σ^4,λ^5-phospholes **41** (Scheme 27) at the B3LYP/6-311+G** level [61]. From the



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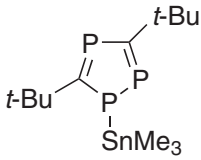

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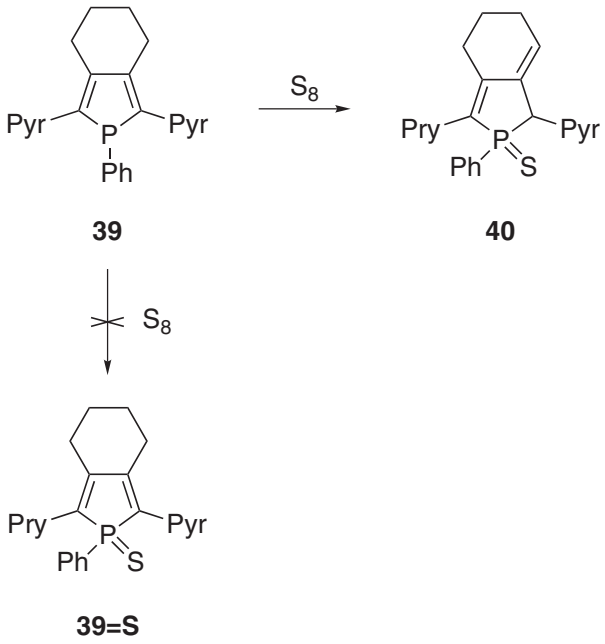
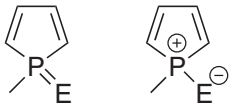
Scheme 25 The stannyl-diphosphole **37** [171] and stannyl triphosphole **38** [172]



Scheme 26 The reaction of phosphole **39** with sulfur [61]



Scheme 27 Hypervalent σ^4,λ^5-phospholes **41** (E: O, S, NH, CH_2) with ylenic and ylidic description

data [61] collected in Table 2 it is evident that with the increasing valence of phosphorus, the slight aromaticity changes to slight antiaromaticity. Also, B3LYP/6-31+G* calculations reproduced the relative stability of **39 = S** and **40**, the latter being more stable by 1.3 kcal mol^{-1}.

Furthermore, although the changes are small, the antiaromaticity increases with the increasing electronegativity of the heteroatom. It is appealing to argue that with the increasing electronegativity of E, the ylidic description of the hypervalent bonding at the σ^4,λ^5-P (**41B** Scheme 27) becomes more pronounced, increasing the positive charge at phosphorus, which results in increased antiaromaticity, leaving only 4π-electrons in the cyclic delocalization.

Comparison of the computed electrostatic potentials (Fig. 4) of phosphole (**41** E: lone pair) and phosphole oxide (**41** E:O) (Hollóczki and Nyulászi, unpublished result) shows that this is indeed the case. The positive charge (shown in red in

Fig. 4) becomes more pronounced at the phosphorus atom in the hypervalent compound. Calculation of the aromaticity% [127] revealed similar tendencies. While phosphole itself exhibits 18% aromatic character, for phosphole oxide -13% has been reported [176]. It is noteworthy that for 1-methoxyephosphole and 1-fluorophosphole small negative values (–4.9% and –9.2%) were also obtained, in agreement with the conclusions of Mathey and coworkers [169]. Also, the phosphole sulfide and selenide exhibited smaller antiaromaticity (–11.6% and –9.7%, respectively) [176] than the oxide, in agreement with the data in Table 2 [61]. It is also worth noting that the decrease of the NICS value and the conjugation upon sulfur addition has been noted in a phosphole–thienyl and a phosphole–pyridyl oligomer by Delare et al. [177].

In the case of phospholium cations **42** (Scheme 28), the positive charge increases further at phosphorus and this should further increase the antiaromatic character.

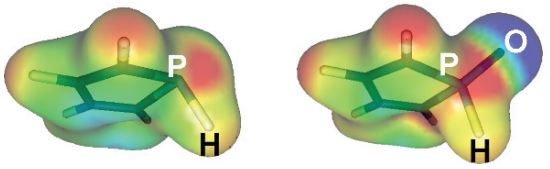
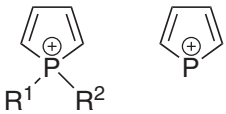


Fig. 4 B3LYP/6-311+G** electrostatic potentials calculated for phosphole (*left*) and phosphole oxide (*right*). *Red* and *blue* colors denote positive and negative charge, respectively (Hollóczki and Nyulászi, unpublished result)

Table 2 ISE, Bird index (BI) and NICS(0) for hypervalent σ^4, λ^5-phospholes [61]

	ISE[a]		NICS(0)
41	(kcal mol–[1])	BI	(ppm)
E: lone pair	–2.6	46	–5.5
E: O	5.7	31	–1.0
E: NH	5.3	25	–1.1
E: S	4.4	33	–2.1
E: CH_2	4.5	32	–1.5

[a] From reaction 9



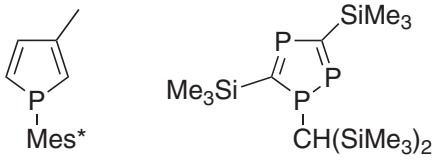
Scheme 28 Phospholium cations **42** and **43** with σ^4- and σ^2-phosphorus, respectively

42 **43**

This is indeed the case, and the ASE for **42** (reaction 8, which was termed homomolecular homodesmotic reaction [170]) dropped from 5.9 kcal mol^{-1} stabilization in phosphole to 5.1 kcal mol^{-1} destabilization in **42** (R^1:H, R^2:H) and 12.3 kcal mol^{-1} destabilization in **42** (R^1:H, R^2:F) [170]. This behavior led the authors to conclude that the presence of the lone pair plays a significant role in the aromaticity of phosphole [170]. It should be noted, however, that in the case of the cation **42**, two σ- and σ*-orbitals (having bonding and antibonding combinations) are available at *both* sides of phosphorus, in contrast to the phosphole case, where the hyperconjugative orbitals are restricted to one side of the ring only, allowing for a less efficient interaction than in the case of **42**.

Further information on the antiaromatic character of **42** can be concluded from the optimized structural parameters of the ring, which were reported for **42** (R^1:H, R^2:H) [178]. The 1.492 Å value at B3LYP/6-31+G** (1.487 Å at B3LYP/6-31G* [179]) reported for the formally single C^3C^4 bond shows some elongation, as compared to phosphole (1.467 Å) itself [178], In the case of the clearly antiaromatic [170] **43**, which exhibits 36.5 kcal mol^{-1} destabilization [170, 178] (measured by ASE – see reaction 8) the length of the same bond is 1.526 Å. The correlation between the C^3C^4 bond length in five-membered heterocycles and ASE has been noted by Chesnut [178]. It should be mentioned that the radical obtainable as a one-electron reduction product from derivatives of **42**, shows increased stability and could be detected by EPR, in some cases even at room temperature [179]. Furthermore, the B3LYP/6-31G* optimized structure of the radical derived from **42** (R^1:H, R^2:H) exhibits equalized bond lengths (CC: 1.39 and 1.42 Å) as a sign of increased cyclic delocalization. The fact that the σ^4-phosphorus cations have similar (although smaller) effects on the aromaticity as their σ^2-phosphorus counterparts has also been observed in the case of the three-membered rings (see above).

While the hyperconjugative interaction can induce some aromaticity in phosphole, the planarization of the σ^3-phosphorus has a significantly larger effect [1–5, 46], in accordance with Mislow's original suggestion [166]. The aromaticity of planar phosphole is larger than that of the other heterocyclopentadienes, including pyrrole and thiophene [33]. However, the intrinsic barrier to planarity of the tricoordinate phosphorus is difficult to overcome. Full planarization of phosphole itself has not yet been achieved, the largest effect being reported for the supermesityl group attached at phosphorus in **44** (Scheme 29), as demonstrated by Keglevich, Quin, and coworkers [180]. The bond angle sum at the σ^3-phosphorus increased in this compound to 331.7° and, in accordance with that, the Bird index in **44** increased to 57 (compared with 46 for the parent phosphole). Most interestingly, **44** has shown S_E reactivity on the phosphole ring [180]. Full planarization, however, was first achieved for triphosphole **45**, benefiting from the planarizing effect of the σ^2,λ^3-P atoms in the ring (see below), the bulky group attached to the tricoordinate phosphorus, and the π-electron withdrawing property of the silyl substituent [181]. The fully planar (SBA about the tricoordinate phosphorus 358°) triphosphole exhibited equalized PC bond lengths, a BI of 84, and BDSHRT 60 [181]. All these observations indicate a very large aromatic character, together with the –12.3 ppm B3LYP/6-31+G* NICS(0) value (Nyulászi, unpublished result) . Another example



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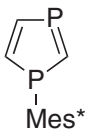

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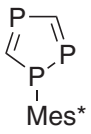

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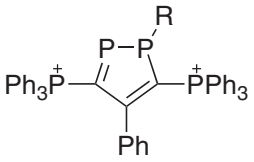

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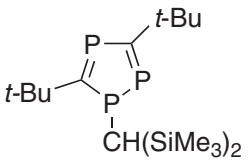
R: Me, Ph



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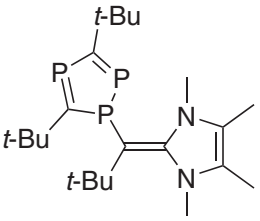

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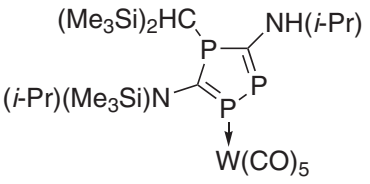


51

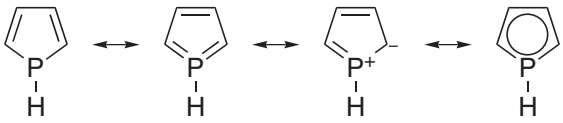
Scheme 29 The synthesized flattened or planar phospholes, diphospholes, and triphospholes

of a nearly fully planar diphosphole (bond angle sum at the tricoordinate phosphorus 352°) has recently been reported [182]. **46** is interesting since it has no other substituent than the bulky Mes* at the tricoordinate phosphorus.

It is worth noting that 1-Mes*-1,2,4-1*H*-triphosphole has been predicted computationally as a fully planar, aromatic (NICS(0) –14.7 ppm) compound **47** [183]. The high aromaticity of **45** can clearly be seen from the equalization of the two CP bond lengths, which are 1.732 Å (P=C) and 1.725 Å (P–C) for the two different bonds. The chemical shifts of the two phosphorus signals in **45** are similar (90.83 and 133.8 ppm for the tricoordinate and dicoordinate phosphorus, respectively), and the $^2J_{PP}$ coupling constant was unusually large (528.2 Hz) [182]. Similar NMR characteristics were also reported for **45** [182]. The large coupling constant together with the short PP bond length (2.075 Å) indicate a multiple bond character between the two phosphorus atoms, giving rise to the description of bonding in the planar ring

with resonance structures (Scheme 30). This description, which contains also a σ^3,λ^5-P [182], has been discussed before [4, 33, 184–186] and is in fact a different formulation of the highly delocalized (i.e., aromatic) electronic structure. (It should be noted that, as discussed by Dransfeld et al. [33], the pentavalent formulation of phosphorus does not necessitate *d*-orbital participation in the bonding.) The nearly planar (bond angle sum 339°) diphosphole **48** bearing electron-withdrawing PPh_3^+ groups [185], and **49**, the *t*-Bu substituted analogue of **45** with bond angle sum of 342.5° [187], also exhibit significant bond length equalization. **49** could be complexed in η^5 fashion [188] by $Cr(CO)_3$ and $Mo(CO)_3$. In these complexes, which were the first examples of η^5 complexation mode for a phosphole, further planarization of the tricoordinate phosphorus has been achieved. **50**, which has been obtained from the reaction of 1,3,5-tri-*tert*-butyl-2,4,6-triphosphole and tetramethyl-imidazol-2-ylidene, has also formed a $Mo(CO)_3$ complex showing a planar five membered ring structure, with equalized PC bond lengths as an indicative of electron delocalization [189]. Also, a 1,3,4-triphosphole, **51**, has been synthesized and characterized in solution as a $W(CO)_5$ complex. Although the proper refinement of the structure was hampered because of the severe disorder of the (*i*-Pr)$SiMe_3$ substituents, the phosphorus was flattened and had a bond angle sum of 322°. Furthermore, an Eyring plot from the dynamic NMR measurements indicated an activation barrier of 41.4 kJ mol^{-1} (9.9 kcal mol^{-1}) [190].

The high aromaticity of the planar form of phosphole [4, 33, 46, 167, 184] and the inversion barrier have also been the subject of recent theoretical studies. Schwerdtfeger and coworkers have compared the planarization barriers of group 15 analogues of pyrrole with those of the corresponding divinyl compounds, obtaining a significant decrease in the energy of the transition structure of the cyclic systems in the case of the heavier elements [191]. It is noteworthy too that they revealed a correlation between the (increasing) barrier and the (decreasing) HOMO–LUMO gap [191]. The effect of some selected substituents on the inversion barrier of phosphole has been studied by Delaere et al. [192]. Alkorta et al. have studied the NICS, BI, HOMA of planar and non-planar phosphole at several levels of the theory up to G2. They found that all measures consistently show the increase of aromaticity in the planar form by an average of 254% [193]. Pelloni and Lazzeretti investigated the ring currents induced in C_4H_4AsH and C_4H_4PH by a magnetic field normal to the plane of the four C atoms [194]. The intensity of the ring currents was found to increase by flattening the molecules. The planar structures exhibited stronger diatropicity, as shown by the current density maps and shielding density maps [194]. Johansson and Juselius have used the gauge-including magnetically induced current (GIMIC) method, as a quantitative measure of the strength of the induced current

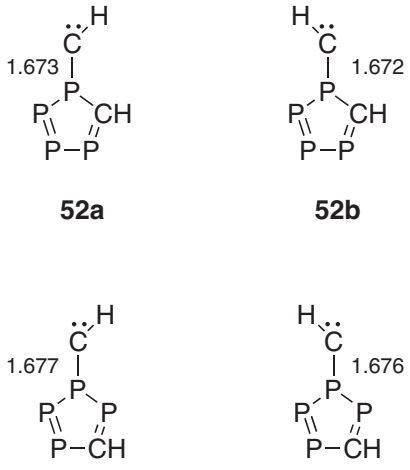


Scheme 30 Resonance structures to describe the bonding situation in planar phospholes

for phosphole and arsole [195]. Together with NICS and the NICS-based ARCS values, the GIMIC results show that the planar form of phosphole and arsole has an aromaticity comparable to that in benzene [195], again in full agreement with the earlier conclusions [4, 33, 184].

As discussed before [4, 33, 46, 186], the incorporation of σ^2,λ^3-P atoms in the phosphole ring reduces the inversion barrier and consequently increases the aromaticity. Pentaphosphole [4, 33, 46, 196–198], which dimerizes in a [4 + 2] fashion with a low barrier [198], is planar and aromatic. The flattening effect can partly be attributed to the electron donor inductive effect of phosphorus [46, 197]. Ring strain effects are also of importance. Incorporation of σ^2,λ^3-P with narrow bonding angles increases the ring strain, which can be alleviated by the 120° bond angle required by the planar sp^2 phosphorus. The chemistry of phosphaphospholes (including diphospharsoles) has been reviewed recently [199, 200]. Further B3LYP/cc-PVTZ computations were carried out on the entire family of phosphaphospholes by Ozimiński and Dobrowolski [201]. The cyclopentadiene-type H(*C*)-phosphole structures (analogous to 2*H*-phospole) are more stable than the H(*P*)-phosphole (analogous to 1*H*-phosphole) in di-, tri-, and tetraphosphaphospholes, except for 1,2,3-triphosphole. The flattening effect of the increasing number of σ^2,λ^3-P atoms in the ring was reproduced [201]. Wang et al. studied ASE, NICS(0.6), NICS(0.8), and bond equalization at the B3LYP/6-311+G** level of a set of five-membered rings including phosphaphospholes, allegedly reproducing all the previously known trends [202].

Skancke and Liebman [203] investigated tetraphospholes, which were found to be non-planar with low inversion barriers, in agreement with other results [33, 201]. The carbene derivatives **52** and **53** shown in Scheme 31 are planar in agreement with [189], and exhibit short PC distances and singlet ground state. Phosphinocarbenes are known to have similar bonding characteristics comparable to P=C double bonds

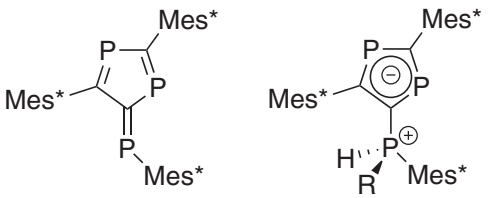


Scheme 31 *P*-carbene-substituted derivatives **52a–b** and **53a–b** of tetraphospholes [203]

[204]. The bonding structure in **52** and **53** was considered to be similar to that in phosphapentafulvenes [203].

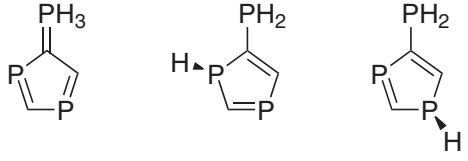
Although the structure of phosphapentafulvenes is described by conventional double bonds, the five-membered ring is prone to accommodate a negative charge, increasing its delocalization. The low lying LUMO of the P=C bonds in the recently synthesized [205] **54** (Scheme 32) further stabilize the zwitterionic charge distribution and the effect is even further corroborated by the presence of the electropositive exocyclic phosphorus. A further enhancement of the charge separation is achieved in **55**, where the exocyclic phosphorus is the positively charged atom of the ylide [206]. The aromaticity of **56** (Scheme 33), which is a model compound for **55**, has been shown by the NICS(0) value of -10.7 ppm to be significant, while the +0.5 ppm NICS value of the model compound for **54** indicates nonaromatic behavior. Interestingly, **55** is a neutral phosphorus-ylide bearing a PH bond, for which only one isolated example was known before [207]. As for the parent $H_2C{=}PH_3$, which is less stable than $H_3C{-}PH_2$ [208], **56** (Scheme 33) is less stable than its isomers **57** and **58** (obtainable by a proton shift from **56**) [206]. This allowed for the conclusion that **55** was kinetically stabilized. It is worth noting that the NICS values of diphospholes **57** and **58** were −4.5 and −5.1 ppm, respectively, and thus the aromaticity of the less stable isomer **56** seems to be larger.

The related family of phosphonio-phospholides also belong to the five-membered aromatic heterocycles, as reviewed comprehensively in the recent work of Gudat [209] The aromaticity of the rings were concluded from stabilization in isodesmic reactions [210] and also from the structure of those rings characterized by X-ray diffraction, exhibiting equalized bond length distribution in the case of the cationic **59** [211] and also for the neutral zwitterionic **60** [212], and its η^1- and η^5-complexed forms [214] (Scheme 34)



54 **55**

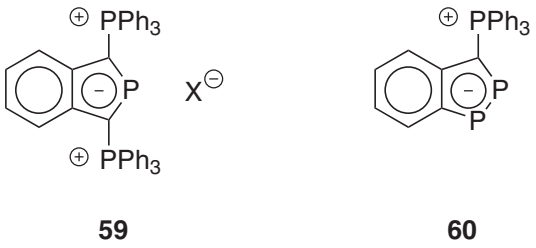
Scheme 32 The triphospa-pentafulvene **54** and the ylide **55**



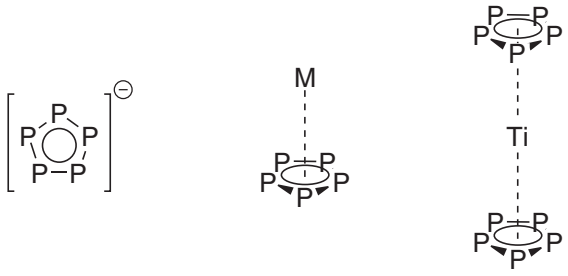
56 **57** **58**

Scheme 33 The phosphorus ylide **56** and the isomeric phosphino-diphospholes **57** and **58**

Scheme 34 The cationic bis-phosphinophospholide **59** and the neutral zwitterionic phosphinophospholide **60**



59 **60**



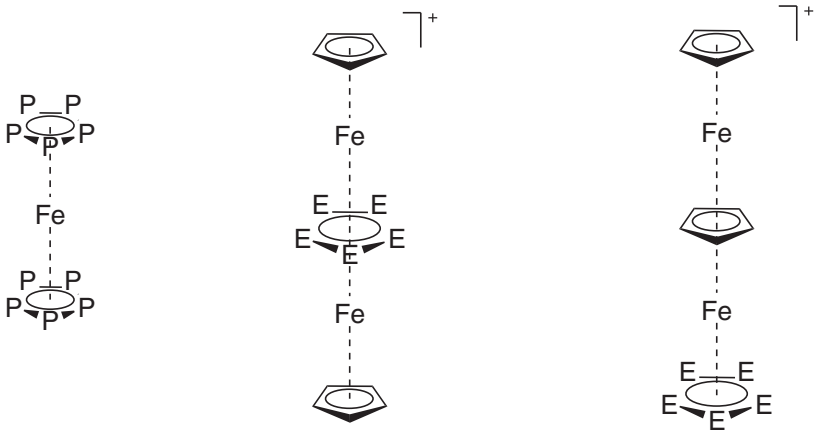
61 **62** **63**

Scheme 35 Pentaphospholoyl anion **61**, η^5-complexed MP_5 (M: Li, K, Na) **62**, and $(P_5)_2Ti$ **63**

All the phospholide anions, which are the phosphorus analogues of the cyclopentadienyl anion [32], were shown to be aromatic [214] and this conclusion has remained unchanged even using more sophisticated levels of the calculations [33]. Among the possible anions, the aromaticity of P_5^- has been studied intensively. The aromaticity of P_5^- **61** (Scheme 35) and As_5^- have been analyzed together with several inorganic ring systems at the B3LYP/6-311+G** level of the theory [215]. While NICS(0) is –18.5 and NICS(1) –18.3 ppm for P_5^-, for As_5^- somewhat larger values of –20.5 and –19.5 ppm have been obtained. The flat NICS height profile indicates that the s electrons contribute to the overall diatropicity of the current density pattern. This is in agreement with the conclusion of Kraus and Korber [153], who have analyzed the ELF properties and noted the importance of σ-contributions. As in the case of the P_4^- ion, they have used the term "lone pair aromaticity." The current density plot analysis at 1 Å exhibits the classical example for a diatropic ring current [215]. The aromaticity of the P_5^- anion and that of the P_5M (M: alkali metal) clusters have been analyzed investigating the MOs and NICS [216]. The most stable form is the C_{5v} η^5-complexed structure **62** (Scheme 35). The NICS shows a significant aromaticity in both the anionic ring and the complexes. Note that the GIAO-B3LYP//B3LYP/6-311+G* NICS value of the anion itself is reported to be more negative by 3.5 ppm than in [216] (reported NICS(0) values are as follows: P_5^- –22.0, P_5Li –18.8, P_5Na –16.0, and P_5K –18.9 ppm) [216]. Together with optimization of the structure, photoelectron spectroscopic investigation of the P_5M clusters was also carried out [217]. The first characterized carbon-free sandwich complex $[(\eta^5\text{–}P_5)_2Ti]$ (Scheme 34) also contained P_5 rings [218]. The ring structure

concluded from the X-ray structure is slightly distorted (PP bond lengths vary between 2.147 and 2.171 Å) [218]. It has been noted in a subsequent computational study that the PP distances are equal in the anion as well as in the Ti complexes, thus the distortion of symmetry found in the X-ray structure was attributed to crystal packing effects [219]. The aromaticity of **63** has also been analyzed by investigating NICS and the contribution of the different orbitals thereof [219]. The –36.8 ppm NICS value of **63** indicates a significant aromaticity; however, the TiP bonding orbitals have a large contribution, as concluded from the dissected NICS investigation.

The structure and aromaticity of the ferrocene analogues $(P_5)_2Fe$ (**64**) and P_5FeCp have been studied by Malar [220]. The aromaticity of the five-membered rings, on the basis of a geometry-based index, in the complex was found to be 66% that of the free ligand for the cyclopentadienyl and 45% that of the free ligand for the pentaphospholoyl ligand rings [220]. The cationic triple-decker complexes **65** and **66** with E_5 rings (E: P, As) were also the subject of computational studies [221]; structure **65** was more stable than **66**. The EE distances in the middle ring (**65**) are longer than in the terminal ring in **66** (for E: P the PP distances are 2.170 and 2.140 Å, respectively). This behavior was attributed to a decreased aromaticity in the middle ring [221].

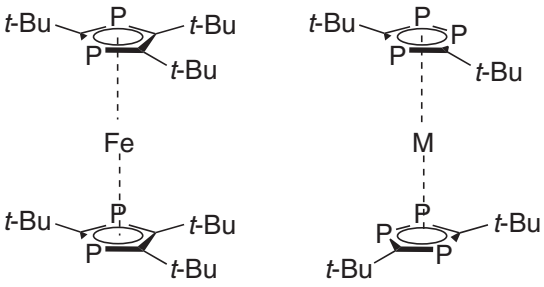


64 **65** **66**

Complexes of diphosphole and triphospholes have also been investigated. The successful synthesis of $(C_3tBu_3P_2)_2Fe$ **67** and $(C_2tBu_2P_3)_2Fe$ **68** (Scheme 36) allowed a study of the photoelectron spectra of these species [222]. Coupled with density functional studies, the electronic structure could be described, and showed a significant sp mixing [222]. Also, the replacement of CR units by P results in increased electron acceptor properties. Mono- and diphosphaferrocenes have been shown to be building blocks for π-conjugated systems [223]. It is interesting to note in this respect that 1,1′-ferrocenylene-diphosphenes were also recently reported [224].

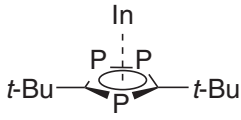
These compounds can also serve as building blocks for phosphorus-containing p-conjugated systems. Not only can *d*-elements form sandwich complexes, but main group metal (In, Ga, and Tl) complexes derivable from the triphospholide anion $P_3C_2{}^t Bu_2$ have also been reported [225–227]. An electron diffraction/DFT study of the triphosphole complexed with indium **69** revealed an η^5 structure (Scheme 37) with a planar five-membered ring [228]. The lengths of the two PC bonds are 1.771 and 1.765 Å, showing the high degree of the bond length equalization. For a recent summary on phospholyl complexes with more examples on coordinated compounds see the review of Le Floch [229].

Very recently, two reports have appeared on benzocondensed derivatives of the 1,2,3-triphospholyl anion **70** [230] and its arsenic **71** (E: As) [231] and antimony **71** (E: Sb) [231] analogues (see Scheme 38). The computed NICS(0) value for the



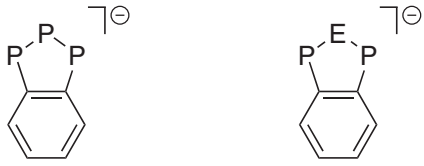
67 **68**

Scheme 36 Sandwich complexes **67** and **68**



69

Scheme 37 η^5-Complexed In-containing complex **69** derived from $P_3C_2tBu_2^-$



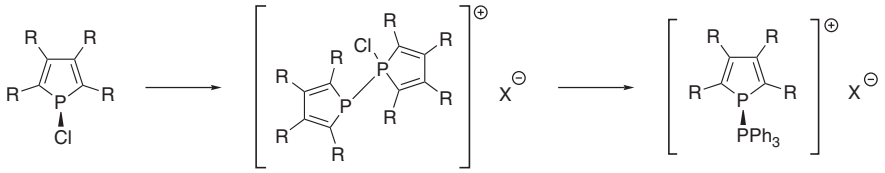
70 **71**

Scheme 38 Benzocondensed tripospholoyl ion **70** and its As and Sb analogue **71**

five-membered ring is -11.7 ppm, which indicates significant aromaticity. However, it is somewhat reduced with respect to the carbon analogue (NICS(0) 13.7 ppm) [230]. In the case of the antimony compound **71** (E: Sb), the one-electron reduced radical dianion should form, as concluded from its X-ray crystallographically characterized dimer [231].

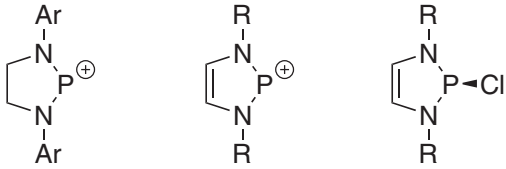
It has been noted before that **43** is antiaromatic, as shown by destabilization in ASE [170, 178]. Furthermore it is among the least stable possible isomers, in contrast to its all-carbon analogue [232]. To reduce the instability, the cation (whose synthesis from a 1-chlorphosphole was attempted) is complexed by nucleophiles, either by the reagent itself (**72**), or by other phosphines (**73**) [233] (see Scheme 39). Note that the reactivity of phosphenium ions towards amine and phosphine nucleophiles has been extensively studied, as reviewed by Burford [234]. The exchange of the phosphines was shown to be an S_{N2} type process from analysis of the reaction kinetics monitored by NMR spectroscopy and ONIOM calculations. In contrast, phosphine exchange in the case of the cation **74** (Scheme 40) was reported to be of S_{N1} type [235]. Furthermore, the PP bond in the phosphine complex formed from **74** was shown to be 0.2 Å longer [235, 236] than for **73** [233]. It has been argued that **43** behaves as a Schrock-type carbene and that the behavior of **74** is related to Fisher-type carbenes, which have singlet ground state (the empty *p*-orbital on the divalent carbon is stabilized by the nitrogen lone pairs of the amino group).

Further stabilization of 1,3,2-diazaphospholane cations can be achieved by incorporating the N–P(+)–N unit in a 6π system, resulting in an electronic structure analogous to the Arduengo carbene [30, 237–243]. It has been shown that while the most important stabilizing effect is exerted by the amino groups on the phosphenium center, the 6π-delocalization indeed has a contribution [30] to the stability of these systems. It is of further interest that the diazaphospholes derived from the



72 **73**

Scheme 39 Synthesis of phosphine–phosphenium cations

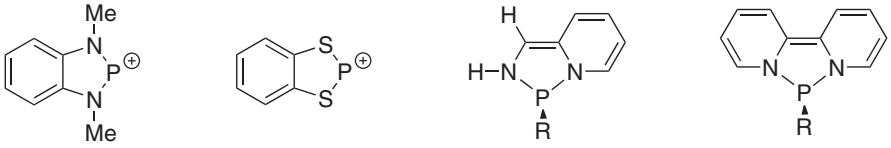


74 **75** **76**

Scheme 40 Diazaphospholenium cations **74**, **75**, and **76**

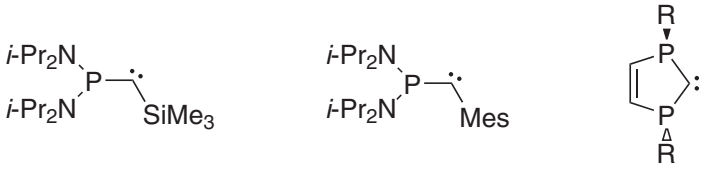
diazaphospholenium cations and an anion (e.g., Cl^--**76**) might also exhibit some hyperconjugative aromaticity. A related phenomenon results in the lengthening of the PP bond in the phosphine complex of **74** [235, 236], as discussed above. Although a systematic study on the delocalization on benzocondensed system is unknown as yet, such systems (**77** [244] and **78** [245, 246] – see Scheme 41) are known. Another mode for the formation of an annelated phosphorus-system can be realized in **79** and **80**. These annelated systems are destabilized with respect to **76** due to the formation of the 7π-system in the six-membered rings [247]. This destabilization results in the weakening of the PN bonds, resulting in their easy dissociation and providing a way for phosphinidene generation. Thus, by selection of the appropriate chemical environment of the phosphenium cation the properties, including chemical reactivity, can be tuned over a wide range.

Not only can the empty orbital of the phosphonium cation be stabilized in five-membered rings, but also the empty orbitals of carbocations and carbenes can be successfully stabilized by neighboring phosphorus lone pairs under proper conditions. The parent phosphinocarbene H_2PCH is planar [248] and has a singlet ground state.The bonding characteristics show similarities to the P=C double bond [249] due to the formation of a π-type dative bond between the lone pair of the (planar) phosphorus and the carbene. Substitution by a silyl group at C opens up the PCSi angle [204, 251] and the structure of the first phosphinocarbene synthesized, **81** [251], has been discussed as having a λ^5-P≡C bond instead [252, 253]. The term push–pull carbene was introduced later [15] to describe the bonding in **81**, and subsequently a persistent phoshinocarbene **82** with a spectator substituent at the divalent carbon was also reported [254]. The phosphorus analogue of the Arduengo-type NHC carbene **83** (Scheme 42) has been predicted by Schoeller [255] to be a



77 **78** **79** **80**

Scheme 41 Annelated ring systems **77**, **78**, **79**, and **80** containing the diazaphosphole or diazaphospholenium unit



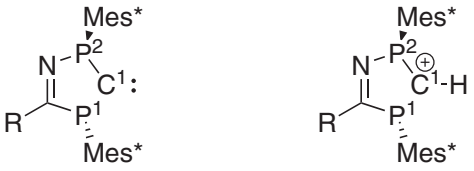
81 **82** **83**

Scheme 42 Phosphinocarbenes **81** [251], **82** [254], and **83** [4, 25, 256, 257]

stabilizable compound, despite the nonplanarity of the tricoordinate phosphorus, since less than 10 kcal mol^{-1} was computed for the energy of the double planarization. Amino substituents at phosphorus were predicted to have further stabilizing effects [256]. As for phospholes [180], the bulky supermesityl group has a beneficial planarizing effect; the presence of planar phosphorus is favorable for the formation of a stabilizing aromatic electronic structure [46]. The NICS(0) value of –15.9 ppm was reported [4] for **83** (R: Mes*) indicating a significant aromaticity, although the tricoordinate phosphorus atoms are not fully planar. It is worth noting that some phospholes also exhibit significant aromatic stabilization even without fully planar tricoordinate phosphorus [180], as discussed above. Apparently the overlap between the π-system and the phosphorus lone pair becomes sizeable even before reaching full planarization. Furthermore, the interaction with the antibonding combination of the *two* neighboring phosphorus lone pairs was proven to be effective even at higher pyramidalization [160]. The planarizing effect of annelation with six-membered rings was also shown to have some effect on the stability of the carbene [257].

In accordance with the above results, the cyclic diphosphinocarbene **84** (R: Me) has been reported together with its precursor carbocation **85** (R: Me), as shown in Scheme 43 [258]. Like the computed structure of **83** (R: Mes*), neither **84** (R: Me) nor **85** (R: Me) are fully planar; however, the phosphorus centers are significantly flattened (bond angle sums are at 350°). The PC^1 bonds in the X-ray structure of both compounds exhibit a significant multiple bond character (the nonequivalent PC distances vary between 1.673 and 1.720 Å for the two compounds) [258]. In a subsequent paper [259], two further derivatives of **85** (R: Ph and NMe_2) were reported. The presence of the dimethylamino substituent is particularly noteworthy. The crystal structure of **85** (R: NMe_2) [259] exhibits significantly shortened NP^2 (1.636 Å) and C^1P^2 (1.646 Å) bonds, suggesting that the bonding be described as σ^3,λ^3-P^1 and σ^3,λ^5-P^2. In the $GaCl_3$ complex of **84** (R: Me) the P^1 atom is planar (σ^3,λ^5-P), while P^2 is somewhat pyramidal [259]. (Note that in 1,3-diphosphete-2, 4-diyls the bonding situation could similarly be shifted between the σ^3,λ^3-P^1 and σ^3,λ^5-P^2 and the σ^3,λ^3-P^1 and σ^3,λ^3-P^2 cases.) Carbene **84** can be utilized as a ligand on transition metals for catalytic purposes.

Computations on its ruthenium complex revealed that upon complexation the pyramidalization of the phosphorus atoms increases [260] as a result of a π-interaction with the transition metal [261]. This indicates that although the variation of the aromaticity in the complexed form of **84** has not been investigated in detail, its



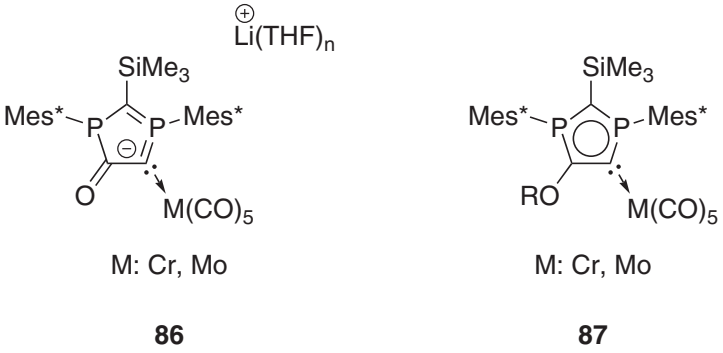
84 **85**

Scheme 43 The synthesized cyclic diphosphinocarbenes **84** and the corresponding carbocations **85** [262, 263]

subtle changes can be related to the activity of catalysts. Before the synthesis of the free carbene **84** itself, Zr and Ti complexes of the perphenyl derivative had been reported [262]. However, in the absence of suitable crystals no structural characterization was carried out and no further information about the aromaticity of this compound is revealed.

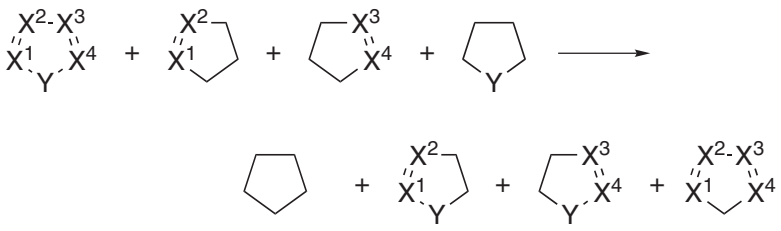
Further phosphinocarbene complexes **86** and **87** (Scheme 44), formed with $Cr(CO)_5$ and $Mo(CO)_5$ derivable from a 1,3-diphosphole ring, were also recently reported [263]. **87** was obtained from **86** by a treatment with RX (X: halogen). **86** exhibits two different phosphorus atoms While the σ^3,λ^3-P is flat, the bond angle sum at the σ^3,λ^5-P is 340°, indicating a partial flattening. The bond length distribution is in accordance with the description given for **86**. Substitution of the oxygen, however, results in a further equalization of the bond lengths, resulting in a Bird index of 76 for R: Me and 71 for $SiMe_3$, a sign of significant aromaticity for the complexed carbene [263].

Heterophospholes are five-membered rings, with additional heteroatoms apart from phosphorus, which is involved in a σ^2,λ^3-bonding. In recent reviews many aromaticity data have been compiled for these systems. The ASE was calculated using the properly balanced equation [56] (Scheme 45) for the five-membered rings in the review paper of Cyranski [64]. The stabilization energies of the



86 **87**

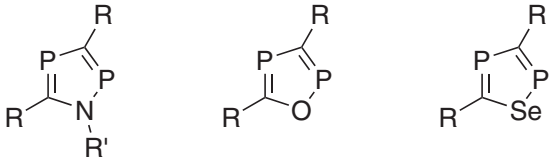
Scheme 44 Cr and Mo complexes of cyclic phosphinocarbenes **86** and **87** [263]



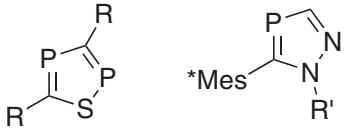
Scheme 45 The properly balanced homodesmotic ASE reaction for five-membered rings with multiple heteroatoms [56]

analogous compounds differing by the replacement of CH unit(s) by P are close to each other, as in the previous observations [4] for polyphospha derivatives. However, some decrease of the stabilization energies with respect to their parent systems can be concluded. Interestingly, the analysis of the NICS data compiled for a similar set of compounds in the same thematic issue of *Chemical Reviews* [48] by Schleyer and coworkers [83] suggests that the NICS values of the phosphorus analogues with three or four P atoms in the ring are somewhat more negative than those of their carbon-containing congeners. For one and two P atoms in the five-membered ring, the NICS values mainly shift toward slightly more positive values. Recalling the results of Korber and coworkers on the P_4^{2-} and P_5^- rings, who reported a significant contribution of the in-plane lone pairs in the ELF analysis [153] using the phrase "lone pair aromaticity" (see above), it is possible that the contribution of the in-plane phosphorus lone pairs to NICS is responsible for the above observation.

Further reports on the aromaticity investigated in conjunction with new synthesized heterophospholes are also in accord with their aromaticity (Scheme 46). The 1-pheny-3,5-di-*tert*-butyl-1,2,4-azadiphosphole **88** (R: *t*-Bu, R′: Ph) exhibited equalized bond lengths (PC bond lengths were between 1.697 and 1.746 Å). A comparison of the B3LYP/6-311+G** computed NICS(0), BI, and BDSHRT values of **88**, **89**, and **90** (R: H, R′: H) with the corresponding parameters for pyrrole, furan, and thipohene, respectively, has shown a small, but consistent, decrease in all these aromaticity measures of the phosphorus derivatives [264]. The reactivity of **89** (R: Mes) has been compared to that of **90** (R: *t*-Bu) in a [4 + 2] cycloaddition

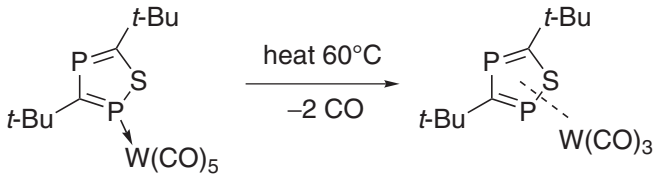


88 **89** **90**



91 **92**

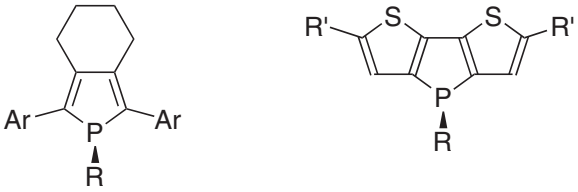
Scheme 46 Recently published heterophospholes with reported aromaticity properties



Scheme 47 Conversion of the η^1-$W(CO)_5$ complex of **91** (R: *t*-Bu) to the η^5-$W(CO)_3$ complex [266]

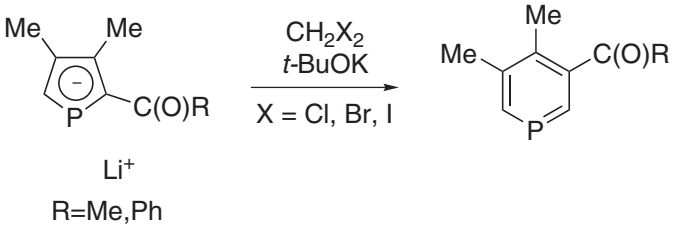
with acetylenedicarboxylate. While **89** (R: Mes) has reacted at –20 °C (in pentane), **90** (R: *t*-Bu) reacted only in boiling toluene, although on the basis of the different steric bulk of the substituents an opposite behavior could be surmised. The observed reactivity, however was related to the difference in the aromaticities of the two rings. The NICS(0) of the parent selenadiphosphole was –12.7 ppm, while that of oxadiphosphole was –11.0 ppm [265]. In a study on the complexing ability of 1,2,4-thiadiphosphole **91** (R: *t*-Bu), both η^1- and η^5-complexation could be achieved with Mo and W carbonyls. Furthermore, the entropy-driven conversion of the η^1- to the η^5-complexed form has also been observed (Scheme 47) [266]. While no suitable crystals could be grown from the η^5-W-complexed form of **91** (R: *t*-Bu), the analogous Cr complexes of the parent ring **91** (R: H) has been studied computationally [266]. It has been noted that the bond length equalization increases upon η^5 complex formation, as in the case of the triphosphole **49** [188]. It is worth noting that thiadiphosphole **91** (R: *t*-Bu) reacts with *t*-BuCP in a [4 + 2] cycloaddition, whereas **49** did not show such reactivity [188]. This difference, however, may also be attributed to the steric shielding of the $CH(SiMe_3)_2$ substituent attached to the σ^3-phosphorus. As a hint for aromaticity in the recently synthesized Mes*-substituted diazaphosphole **92**, the signals of the *o-tert*-butyl groups in the ^{1}H NMR spectrum showed a shift to a higher field, because of the aromatic character of the ring [267]. The chemistry of benzannelated heterophospholes has been reviewed by Bansal and Heinicke [268].

The research of π-conjugated organic materials containing phosphorus is a rapidly growing area and has been reviewed recently [50]. Most of the work in this area is related to the five-membered ring phospholes [50, 51]. Apart from oligophospholes, where the phosphole units are linked directly, the mixed systems with a phosphole central unit attached to other aromatics **93** (Ar: Ph, pyridyl, thienyl) [269, 270] have been explored in detail. Also, the properties of the annelated dithieno[3,2-*b*:2′,3′-*d*]phosphole system **94** [271, 272] has been explored in detail. The fact that the LUMO levels of phosphole can be effectively tuned by variation of the hyperconjugative interactions [273] results in changes of the aromaticity [61, 177] of the central phosphole unit (as discussed above) and allows for variation of the inter-ring conjugative interactions, resulting in variations in the photophysical properties. Likewise, in the case of the annelated ring system **94**, which has increased BI values in *both* phosphole and thiophene rings as a result of the extended conjugation [274], fine tuning of the properties by modifications at



93 **94**

Scheme 48 Conjugated five-membered ring systems with phosphorus, having potential photophysical applications



Scheme 49 The one-pot conversion of the phospholide ion to phosphabenzene [278]

phosphorus is also possible. In a recent study, the structure of the first excited state of some derivatives of **93** has also been optimized by CIS [275]. The relationship between the energy levels (tunable by substitution at phosphorus) and physical properties, as well as aromaticity and delocalization, has been noted [276, 277]. It remains for the future to see whether a quantitative relationship between aromaticity measures and photophysical properties can be established or not (Scheme 48).

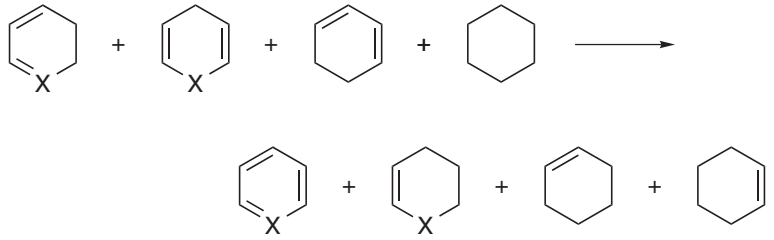
A final remark to close the section dealing with five-membered rings is that Mathey recently reported a one-pot procedure converting a phospholide ion (which is highly aromatic, as discussed above) to the six-membered ring phosphabenzene (which is also highly aromatic, as will be discussed below) as shown in Scheme 49 [278].

5 Six-Membered Rings

The aromaticity of the six-membered ring phosphinine is similar to that of benzene (different aromaticity measures all exhibit about 90% of the benzene values), as reviewed previously [4, 278]. These characteristics reflect in the frequently used term “phosphabenzene” (for a recent review on its chemistry, coordination, and catalytic behavior see [279]). The numerical values for some aromaticity indicators

Table 3 Aromaticity measures of benzene and phosphinine (phosphabenzene)

	ASE (Kcal mol–1	NICS(0) (ppm)	NICS(1) (ppm)	NICS(0)π (ppm)	HOMA	BI	BDSHRT
	32.7	–8.9	–10.2	–20.7[a]	0.995	100	67
	28.1	–8.1	–9.7	19.1[b]	0.9737	96	62
Ref	[283]	[4]	[283]	[a][78] [b][284]	[283]	[4]	[4]



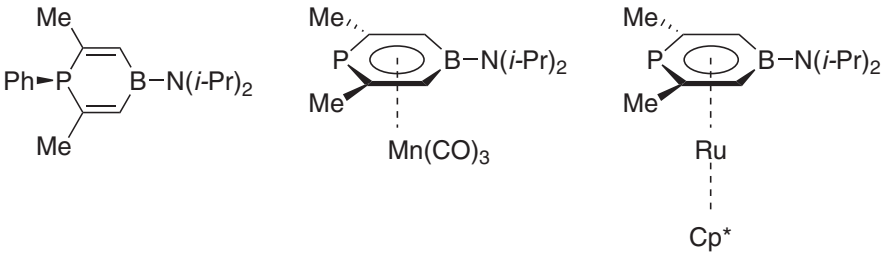
Scheme 50 The selected reaction [280] for the definition of ASE

are compiled in Table 3, including those obtained recently [280] at the B3LYP/6-311++G** level. The reaction selected to estimate ASE values is shown in Scheme 50 [280]. In a different study, Salcedo [281] has shown that the aromatic stabilization energy in a homodesmotic reaction with respect to open chain references is the largest among the pyridine homologues. Frenking, who used the method of energy decomposition analysis (EDA), has shown that the stabilization in pyridine is larger than in benzene, followed by phosphinine [282]. Bacharach studied the geometric data, NICS, and resonance energies of benzenes, pyridines, and phosphinines annulated by small rings to investigate the Mills–Nixon effect. He showed that the cyclopropa systems are aromatic, the cyclobutanana systems express some aromaticity, and the cyclobutena systems are not aromatic [283].

However, the reactivity of the phosphinines is somewhat enhanced in comparison with benzene. Not only the lone pair at P is a reactive center, but phosphorus can also be attacked by electrophiles to form hypervalent compounds. Furthermore, stabilization of the unoccupied levels, which was discussed in conjunction with the electron transmission spectra of phosphinine and 1,3,5-triphosphinine [14], also allows for an easy nucleophilic attack [4, 279].

Substitution of the CH units in the ring by P or N results in some variation in the aromaticity. Azaphosphinines have been considered somewhat less aromatic than benzene, pyridine, or phosphinine according to NICS(0.5) values [284]. With N atoms at the position adjacent to P, the aromatic delocalization is reduced and a [1,4] dipolar character is induced [284]. The NICS(0) values of diphosphinines

were reported to be somewhat less negative than for phosphinine itself [285]. In an investigation of the vibrational frequencies and the MOs of the planar sym-P_3N_3 ring, the aromatic character was concluded from the MOs. However, investigation of the bond lengths suggested little double bond character and therefore "little true aromaticity" [286]. As for diphosphinines, the phosphapyridines exhibit less negative NICS values with the increasing number of phosphorus atom in the ring [83]. The aromaticity of triphosphinine has also been investigated [4, 42, 287] and was found significant, in spite of the apparent ring strain due to the narrow bonding angles about phosphorus. It is worth noting that most of the synthesized polyphosphabenzenes have *t*-Bu substituents at the carbon atoms. The destabilization of two *t*-Bu groups at neighboring carbon atoms was shown to be about 22–25 kcal mol^{-1}, which is comparable to the stabilization in rather aromatic systems [288]. This is in accordance with the stability of the well investigated symmetric 2,4,6-tri-*tert*-butyl-1,3,5-triphosphabenzene. Among other inorganic benzenes, the planar form of P_6 has also been investigated [289]. In a VB (valence bond) description, a resonance energy of 47 kJ mol^{-1} (11.2 kcal mol^{-1}) has been reported, which is less than the 81 kJ mol^{-1} (19.4 kcal mol^{-1}) reported for benzene [289]. The extent of aromaticity was also investigated by a method that is a combination of the configurational interaction, localized MO, and CASSCF analyses [290], resulting in sizeable stabilization in the case of P_6. It has also been concluded that the extent of aromaticity is related to low electronegativity [290]. Substitution of the ring carbon atoms by boron creates a vacant orbital in the ring, thus 6π-systems can only be achieved by introducing σ^3-phosphorus atoms in an equal number to the boron atoms. $P_3B_3H_6$ has been investigated before and, as summarized in [4], the parent $B_3P_3H_6$ deviates slightly from planarity, and the planar form exhibits some aromaticity. In the recent VB study [288] this was the only mixed compound that exhibited a certain aromaticity, in accordance with previous results [4, 78, 291], and can be explained by the similar electronegativities of boron and phosphorus. The rings synthesized with a B_3P_3 skeleton are substituted by bulky groups (Mes* and cyclohexyl in the case of the first reported derivative [292]) and are planar. A further interesting aspect is that they form a η^6 complex with $Cr(CO)_3$ [293]. The recently synthesized 1,4-phosphaboratabenzene derivative **95** (Scheme 51), featuring an $(i\text{-Pr})_2N$ group at boron,



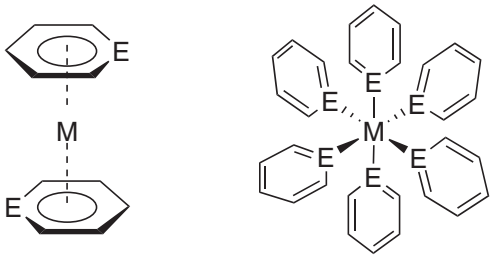
95 **96** **97**

Scheme 51 1,4-Phosphaboratabenzene derivative **95**, and its aromatic η^6-complexes **96** and **97**

exhibits non-delocalized structural characteristics. However, it can be η^6-complexed with $Mn(CO)_3$ (**96**) and RuCp* (**97**), upon loss of the phenyl substituent of phosphorus. The resulting structures exhibit significant bond length equalization (e.g., the CC bonds are about 1.40 Å) [294].

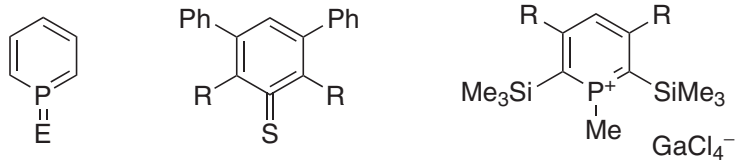
The η^6 coordination, which is characteristic for aromatic systems (Scheme 52), is also known for phosphinine **98** (E: P); however, it rivals the η^1 **99** (E: P) [229, 295], and even more curious [296] complexation modes. For the parent phosphinine, the η^6 coordination was achieved for the vanadium complex **98** (E: P, M: V) [297]. However, 2,4,6-tri-*tert*-butyl-phosphinine, where the bulky groups protect the η^1 position, also coordinates chromium in η^6 fashion [298]. Interestingly, in a recent work it has been shown that arsinine (C_5H_5As) coordinates Mo both in η^6 **98** (E: As, M: Mo, Cr) and in η^1 **99** (E: As, M: Mo W) mode [299]. The η^6 complexes of alkali (Li^+, Na^+, K^+) and alkaline earth (Mg^{2+} and Ca^{2+}) metals with mono-, di- and triphosphinines has been investigated. The energy of the complex formation did not correlate with NICS [300]. The coordination behavior of 2,6-disilyl-substituted phosphinines towards Au(I) has been studied. From the X-ray structure of the complex a slight reduction in the aromaticity of the phosphinine ring has been concluded as a result of the poor π-back bonding ability of the AuCl fragment [301].

The P atom of phosphinine can also be substituted by main group elements resulting in **100** (Scheme 53). The substituents can be O, S, Se, NR, and CR_2. **100** features



98 **99**

Scheme 52 η^6- (**98**) and η^1-bonded (**99**) phosphinines



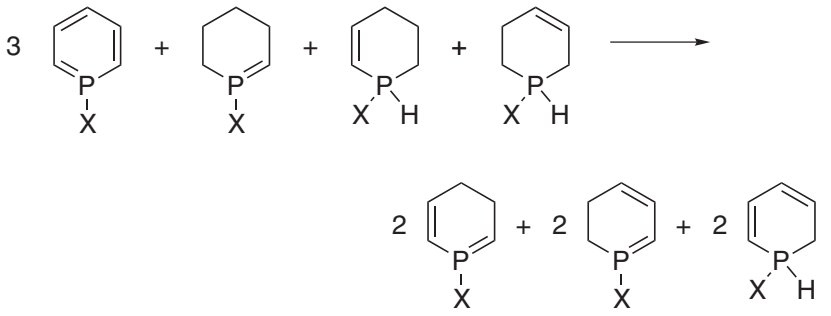
100 **101** **102**

R=Ph, $SiMe_3$

Scheme 53 Derivatives of phosphinine

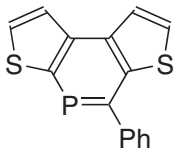
a σ^4,λ^5-bonded phosphorus as shown in Scheme 6. Recently the aromaticity of phosphinine oxide **100** (E: O) and sulfide **100** (E: S) has been investigated [302]. According to the NICS(0), a small increase was observed in aromaticity, while NICS(1) becomes somewhat less negative than in the case of the parent phosphinine [302]. **101**, a derivative of the phosphinine sulfide, has recently been synthesized. The bond lengths from the X-ray structure were also close to that in the phosphinine itself, showing the similar aromaticities of the compounds. Also, the ASE shown in Scheme 54 was comparable for **100** (E: O and S) to that obtained for the parent phosphinine [303].

The P atom can also be attacked by electrophiles, resulting in cations. The proton affinity of phosphinine has recently been thoroughly reevaluated by theoretical means. While the aromaticity issue in the protonated form was not discussed, it is clear that P-protonation is preferred over C-protonation, which would result in nonaromatic systems [304]. The proton affinity (in the gas phase) was 195.8 ± 1.0 kcal mol^{-1}, a value that is far smaller than the corresponding value for pyridine (C_5H_5N) of 219.4 kcal mol^{-1}. The P-protonated form of 2,4,6-tri-*tert*-butyl-phosphinene and that of 2,4,6-tri-*tert*-butyl-1,3,5-triphosphabenzene have recently been synthesized and characterized by X-ray crystallography. The bond length distributions did not differ considerably from those of the parent neutral rings, allowing the conclusion of a high degree of delocalization in both cationic rings [305]. Furthermore, P-silylation of the 2,4,6-tri-*tert*-butyl-phosphinine has been reported. Recently P-methylation of a phosphinine has also been reported [306] furnishing **102** (Scheme 53). The X-ray structural analysis of **102** revealed a planar molecule with equalized bond lengths (CC: 1.407, 1.415 Å; these values are typical for phosphinine). Computations on the model compounds (neglecting the substituents at the ring C atoms) revealed that upon methylation and protonation (at P) neither NICS(0), nor the ASE (defined by the reaction shown in Scheme 54) changes substantially. The aromaticity of the 1-methyl-phoshininium cation itself was concluded from NICS(0) and NICS(1) values, and also using a different homodesmotic reaction with open chain reference structures in a separate work [307]. As for **100** (E: S), the barrier of the [4 + 2] cycloaddition reaction with acetylene is reduced [303, 306].



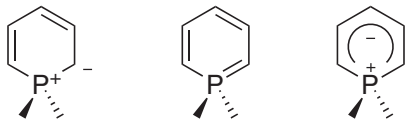
Scheme 54 ASE to evaluate the stabilization energy in phosphinine and its P-substituted derivatives [303]

Like phospholes, phosphinines can also be part of extended π-systems. In a recent work, Mathey et al. have synthesized and characterized by X-ray crystallography a dithienophosphinine **103** (Scheme 55) [308]. The electronic interaction between the fused rings has been shown on the orbitals and by the decreased NICS(1) value (from -10.8 ppm to -8.8 ppm) of the phosphinine ring.

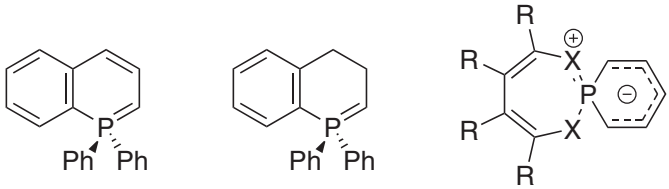


Scheme 55 The dithienophosphinine **103** [308] **103**

In six-membered rings, σ^4,λ^5-P can also be a building block (see Scheme 4). The aromaticity of these compounds has been discussed [4, 42, 125] using different models emphasizing either the delocalization or the ylidic character of the bonding. The stabilization in the six-membered cyclic delocalized system σ^4,λ^5-phosphinine **104** (Scheme 56) has also been shown before [42]. Furthermore, a condensed

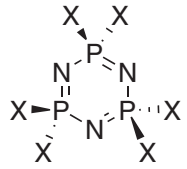


104a **104b** **104c**



105 **106** **107**

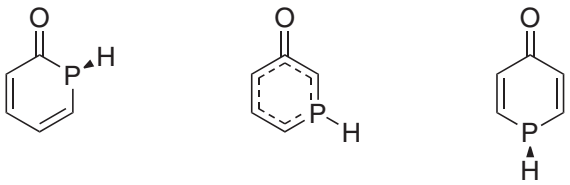
Scheme 56 Six-membered cyclic systems **104a–c**, **105**, **106,** and **107** with σ^3,λ^5-P



Scheme 57 The cyclic phosphazene **108** **108**

derivative **105** did not react in a Wittig reaction, while its saturated analogue **106** reacted in accordance with expectations [309]. In a recent work, Wang and Schleyer computed HF/6-31+G* NICS(1) NICS(0) as well as BI and HOMA values (geometries were obtained at B3LYP/6-31G*) for a series of 1,1-X-σ^4,λ^5-phosphinines (X: F, Cl, Br, OMe, Me, H, SiH_3) [125]. While the BI and HOMA values exhibited similar values to those of the parent phosphinine, the NICS values were significantly smaller for X: Me, H, and SiH_3. For the systems with electronegative substituents, about 30% reduction was shown over the NICS(1) values of phosphinine. The NICS(0)π value obtained for **104** (X: F) was -17.6 ppm, while for **104** (X: H) it was only -2.8 ppm (for phosphinine it is -19.2 ppm; see Table 3). The effective participation of the hypervalent $>PF_2$ groups in (hyper)conjugative interactions has already been discussed for the three-membered ring phosphirenes [99, 111]. Rzepa and Taylor obtained similar results with NICS(1) in the phosphinine ring (from -5 to -7 ppm) for **107**, a spirocyclic derivative of **104** (Scheme 56) where the spirocycle is attached to the phosphinine ring via electronegative X (O, S, or N) atoms [300].

The effect of halogeno substitution at phosphorus has also been studied by Breza [311] on the cyclic triphosphazenes **108** (Scheme 57). He noted that the *d*-orbitals of phosphorus are polarization functions only, and this questions the use of the island model of Dewar [312]. While he stated, arguing with the Dewar model, that phosphazenes are not aromatic, it is worth noting that the optimized bond lengths in **108** (X: F, Cl) are about 0.03 Å shorter than in **108** (X: H). This observation is in agreement with the increasingly effective conjugative interaction of the $>PF_2$ unit, discussed above. The conclusion that **108** is nonaromatic, which is basically in accordance with the conclusion drawn from the island model of Dewar [312], has also been deduced from the topological analysis of the electron density [313], the PN bonding being highly ionic as concluded from the 0.63 shared electron pairs in a PN bond of the ring. In a recent work [314] the NICS values were also reported for the cyclophosphazene **108** and its substituted derivatives. While NICS values for the parent system **108** (X: H) are around zero, with NICS(0) at -5.4 ppm and NICS(1) at –3.0 ppm, **108** (X: F) exhibits some aroma-



109 **110** **111**

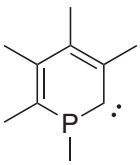
Scheme 58 Phosphorus analogues of pyridone **109–111**

ticity, supporting the use of the negative hyperconjugation model to describe the bonding in these cyclophosphazenes.

The alkylation on the P atom of substituted phosphinines resulted in anionic λ^4-phosphinines [315]. The aromaticity of the ring is significantly reduced according to NMR chemical shift values. Similarly, the adduct of triphosphabenzene with ethyl-magnesium-bromide has been reported to yield an ion pair, which resulted in a nonplanar structure with nonequalized bond lengths [316].

In two recent works the phosphorus analogues of pyridones **109**–**111** (Scheme 58) have been studied computationally [317, 318]. **110** is planar, while for **109** and **111** the planar structures are transition states with 11.0 and 19.8 kcal mol^{-1} above the nonplanar minimum, respectively. The low barriers to inversion indicate that the planar structures have considerable aromaticity, which is shown by the NICS values exhibiting 67%, 51%, and 33% of the benzene value for **109**, **110**, and **111**, respectively [317]. ELF analysis also indicates a certain aromaticity in these compounds [317]. The bonding situation in **109** is similar to the cyclic phosphinocarbene isomer of phosphinine **112** [319] (Scheme 59), which was shown to be planar and aromatic. Stabilization of this carbene can be achieved by incorporating it to an annelated ring system **113**, and also by the electron donor effect of an ylide formed with an additional σ^4,λ^5-P (**114**) [319].

Since a closing statement of the section on five-membered rings was that aromatic six-membered rings can be formed from the aromatic five-membered phospholide rings, it is apparent that reactions in the reverse direction (i.e., the formation of aromatic five-membered rings from the six-membered ones) should also be discussed. 2,4,6-Tri-*tert*-butyl-1,3,5-triphosphabenzene was shown to provide diphospholide ions upon reaction with nucleophiles such as lithium amide [320], alklylithium [321], or alkali metals [322]. Furthermore, the reaction of the same triphosphabenzene with tetramethyl-imidazol-2-ylidene furnishing **50** [189] can be reversed upon treating with $PtCl_2(PMe_3)_2$ to remove the carbene upon complex formation, thus showing the reversibility of the aromatic–aromatic interconversion process.



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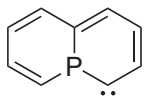

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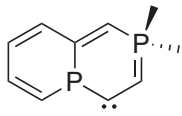

114

Scheme 59 Six-membered stabilized aromatic phosphinocarbenes **112** [319] and **113**–**114** [257]

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Aromaticity and Tautomerism in Porphyrins and Porphyrinoids

M. Stępień and L. Latos-Grażyński

Abstract Porphyrins and their analogues constitute one of the most important families of aromatic macrocycles. The present review discusses aromaticity of porphyrinoids, focusing mainly on non-expanded systems. The effect of structural modifications on the aromaticity-dependent properties of porphyrin-like macrocycles is described. It is shown that delocalization modes observed in porphyrinoids can be classified using a simple valence-bond approach. Aromaticity of porphyrinoids is further discussed as a function of tautomerism, coordination chemistry, and the oxidation state of the macrocycle.

Keywords Aromaticity, Electronic structure, NMR spectroscopy, Porphyrinoids, Tautomerism.

Contents

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1 Introduction and Scope

Porphyrin (**1**), the quintessential pyrrolic macrocycle, is one of the favorite structural motifs of organic chemistry [1]. Its biological relevance, combined with a range of useful properties such as the rich electronic absorption spectra and the ability to coordinate metal ions, makes **1** a versatile building block for the synthetic chemist, as well as an important subject for physical investigations. Among the most conspicuous features of the porphyrin macrocycle is its aromatic character, which has a strong influence on the spectroscopic properties and chemical reactivity of **1** and its derivatives.

Variations on the basic structural theme of **1** have led to a plethora of unusual macrocyclic systems, collectively known as porphyrin analogs or porphyrinoids. These molecules, often nontrivial to synthesize, exhibit remarkable physical and chemical properties and their chemistry has been extensively reviewed [2–18]. With the impressive range of structural modifications introduced so far, the term "porphyrinoid" has ultimately expanded to encompass a wide range of often exotic macrocycles, some of which contain no pyrrole rings at all, or have a structural outline barely resembling that of porphyrin. Some of the generic modification types are shown in Fig. 1. Combination of these design concepts provides a virtually inexhaustible source of structural diversity.

A great number of porphyrin analogs possess circular conjugation pathways, and often exhibit aromaticity comparable with that of the parent system **1**. Moreover, the π-electron delocalization of many porphyrin-like molecules is strongly affected by structural detail, redox chemistry, and prototropic tautomerism. The aim of the present review is to provide a description of porphyrinoid aromaticity and its connection with tautomeric equilibria. Our main focus will be on the physical manifestations of aromaticity, with a special emphasis on NMR spectroscopy. The reactivity of porphyrin analogs, including their coordination chemistry, will be discussed only to the extent it has a bearing on their aromaticity.

To keep the review within reasonable limits, the aromaticity of expanded porphyrins will be discussed only very briefly, mostly to provide examples of certain phenomena. The aromatic properties of expanded porphyrins often depend on conformational effects, and the amount of available data places these interesting molecules outside the scope of the present review. Furthermore, only all-carbon linked systems will be discussed, and nitrogen bridged systems, such as phthalocyanines will not be included.

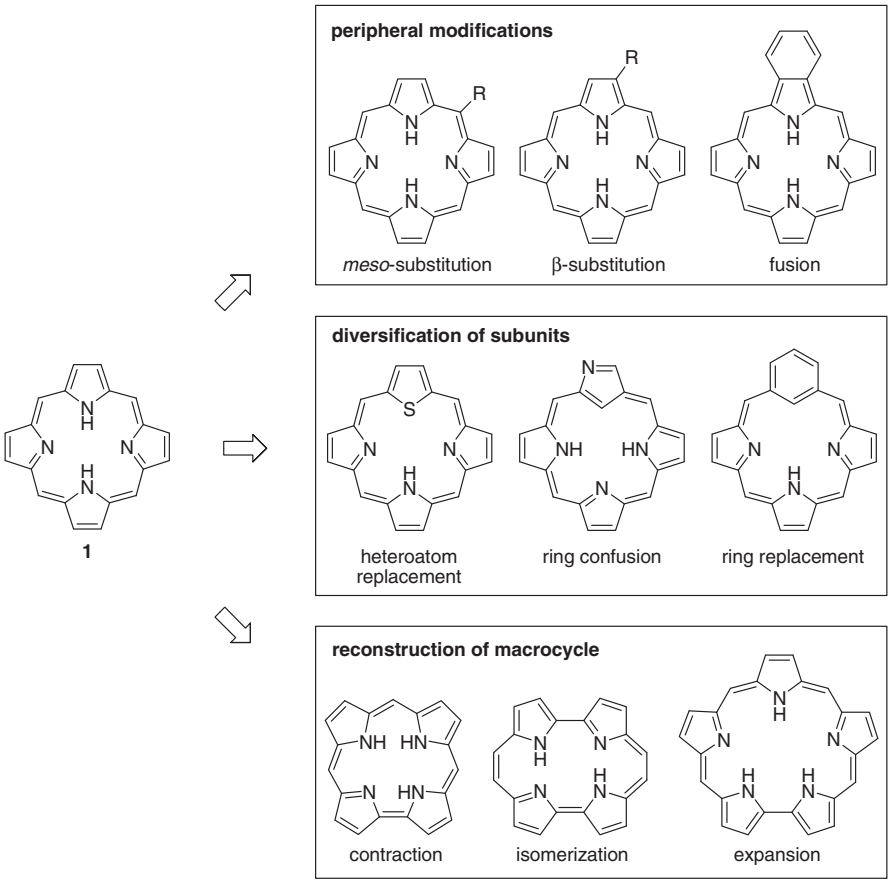


Fig. 1 Structural modifications of the porphyrin ring

1.1 Conventions

1.1.1 Atom Numbering and Substituent Patterns

Most of the porphyrinoid molecules synthesized so far possess a number of peripheral substituents. In fact, many of the important macrocyclic systems were obtained with several distinct substitution patterns. Usually they correspond to one of the generic substitution types of regular porphyrins: *meso*-aryl or β-alkyl, as exemplified by 5,10,15,20-tetraphenylporphyrin and 2,3,7,8,12,13,17,18-octaethylporphyrin, respectively (Fig. 2). For the sake of brevity we will assume the following conventions in the entire manuscript:

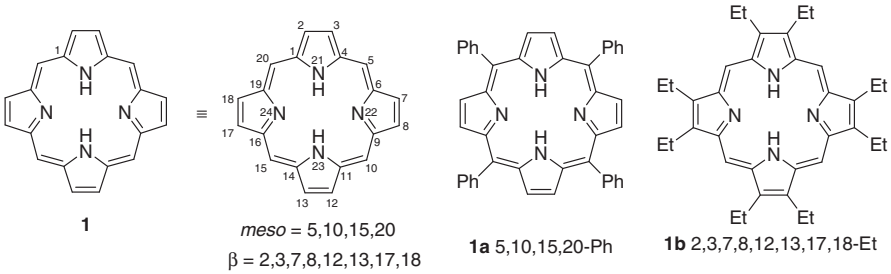


Fig. 2 Numbering scheme and typical substitution patterns in porphyrins

1. Structures of macrocyclic systems will be labeled with consecutive bold numbers, e.g., **1**, **2**, **3**, each number corresponding to a specific ring system. Bold numbers will additionally discriminate between related structures containing different heteroatoms or metal ions, and between different protonation/oxidation levels of the same structure.
2. Different substitution patterns will be labeled with additional lowercase letters, e.g., **1a**, **1b**, **1c**. To save space, structures available in several substitution patterns will often be drawn with no substituents. Instead, the substituents will be listed after corresponding structure symbols. For instance, "**1a** 5,10,15,20-Ph″ corresponds to 5,10,15,20-tetraphenylporphyrin (**1a**). Letter designations will be omitted when: (i) there is just one substitution pattern and it is shown explicitly in the scheme, (ii) no reference to any specific substitution is made.
3. Where necessary, different tautomers (or conformers) of the same molecule will be denoted with an additional number preceded by a hyphen, e.g., **50c-1**, **50c-2**, etc. Different canonical forms of the same structure will be distinguished with primes, e.g., **1**, **1′**, **1″**.
4. The numbering scheme for each ring system is implicit, whenever it can be deduced from the standard numbering convention. According to this convention, peripheral atoms of the macrocycle are first numbered in the clockwise direction, followed by the internal atoms (also clockwise). The first peripheral atom in the sequence is shown in each new structure. The first internal atom is the one adjacent to the first peripheral atom. Systems differing from the above rules are provided with explicit numbering.

The "conjugation pathways" are shown in bold bonds to indicate a circuit of alternating single and double bonds in the molecule, corresponding to a Kekulé pair of canonical structures. These pathways are principally a topological feature of a given valence structure and may correspond to aromaticity, antiaromaticity, or even lack of aromaticity, depending on the properties of the system. This graphical convention will be used rigorously with the exception of type **C** conjugated systems (Sect. 2.1), for which a bifurcated pathway will be shown. Delocalization in charged systems will be denoted with dashed bonds.

1.1.2 Nomenclature

Nomenclature of porphyrinoids freely mixes trivial and quasi-systematic names. A trivial name, such as sapphyrin, which often metaphorically describes the color of the free base or acid salt, normally refers to a generic all-pyrrole structure with no specific substituents, and all its derivatives are named by applying standard nomenclature rules. This is in contrast with Fischer's traditional names of regular porphyrins, which refer to particular substitution patterns (e.g., protoporphyrin). The quasi-systematic naming of porphyrinoids is based on the system proposed by Franck with some modifications [5, 19]. A cyclic conjugated oligopyrrole containing *n* pyrrole rings is called triphyrin ($n = 3$), tetraphyrin ($n = 4$, i.e., porphyrin), pentaphyrin ($n = 5$), etc. This name is followed by a sequence of *n* numbers written as "(*a.b.c.d…n*)," which informs how many *meso* carbons (*meso* bridges) there are between each consecutive pair of pyrrole rings. For instance, porphyrin **1**, with single *meso* bridges alternating with pyrrole rings is named tetraphyrin(1.1.1.1), whereas sapphyrin **48** (Sect. 2.5.1) is termed pentaphyrin (1.1.1.1.0). An additional feature of this naming system, which indicates the conjugation type in the macrocycle (and, indirectly, its oxidation level), will be discussed in the following section.

In the classical description of the porphyrin nucleus **1**, the constituent rings used to be termed "pyrrole" (ring A), "maleinimide" (ring C) and "pyrrolenine" (rings B and D) to reflect the double bond pattern in each ring [20]. However, for greater clarity, we will consistently refer to four pyrrole rings in the porphyrin in spite of their different conjugation and protonation status. Generally, all hetero- and carbocyclic moieties embedded in a macrocyclic framework will be identified by using trivial names of related small molecules with full unsaturation, e.g., furan, or thiophene. As an exception, benzene rings will be referred to as phenylene rings, making it easy to distinguish between different anchoring modes (i.e., *meta*- and *para*-phenylene).

The term "heteroatom" has adopted a nonstandard meaning in porphyrin chemistry. Most generally, it denotes an atom replacing an original atom (C or N) in an all-pyrrole porphyrinoid. Thus the inner nitrogens in porphyrin are not considered heteroatoms but can be replaced with heteroatoms such as oxygen or sulfur. According to this definition, a carbon atom replacing one of the pyrrolic nitrogens is also considered a heteroatom (hence the prefix "carba" used for naming of X-confused macrocycles).

2 Porphyrins and Other Cyclic Oligopyrroles

2.1 The Annulene Model and Related Concepts

The Hückel theory [21, 22], which has become the standard description of annulene aromaticity, is one of the cornerstones of physical organic chemistry. Unfortunately, in its qualitative version, from which the famous Hückel rules are derived, the theory does

not take into account many features of the real aromatic molecules, such as their three-dimensional structure, σ-bonding, or the presence of heteroatoms. Furthermore, the Hückel rules are derived for monocyclic systems, and therefore cannot be directly applied to polycyclic molecules, including porphyrinoids.

Many of the above deficiencies were removed in further refinements of the Hückel method, which was anyway made obsolete by the development of ab initio and DFT techniques. Still, organic chemists adhere to the original Hückel description, which is often sufficient to make qualitative predictions about the nature of π-conjugated systems. In particular, the Hückel model finds widespread use in porphyrinoid chemistry. The so-called annulene model, which will be used throughout this review, is outlined below for the parent porphyrin macrocycle.

The porphyrin ring contains 22 electrons in its π orbitals. As explained above, the Hückel rule cannot be applied to this electron count, because the molecule is not monocyclic. However, the porphyrin ring can be formally derived from neutral [18]annulene, by introduction of appropriate heteroatoms and bridges (Fig. 3). The macrocycle is thus shown to be aromatic in the Hückel sense, and is denoted [18]porphyrin. As we will show in subsequent sections, this approach is readily generalized to other porphyrinoids, whose aromatic character can be predicted by defining a neutral annulenoid pathway in the macrocycle. These pathways will be

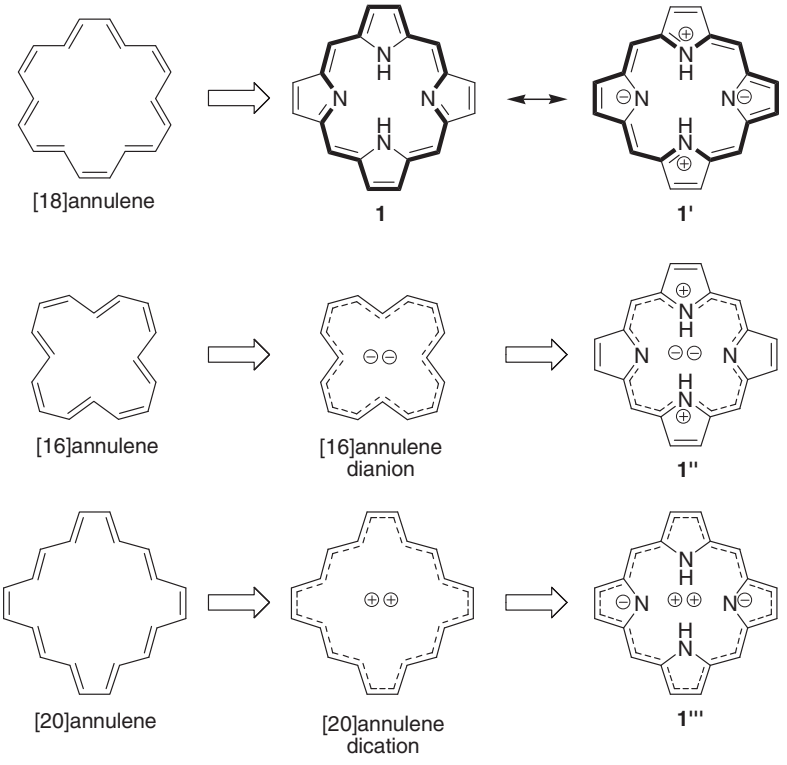


Fig. 3 Annulenoid pathways in the porphyrin macrocycle

denoted with bold bonds, as in Fig. 3. Finally, it should be noted that an alternative [18]annulene pathway **1′** can be proposed, which differs from pathway **1** in the placement of the NH protons, leading to charge separation.

Alternatively, the porphyrin ring can be constructed starting from [16]annulene. In the first step, two electrons are added to form the corresponding [16]annulene dianion, which is transformed into porphyrin (**1″**) by adding bridges and heteroatoms. Unlike the structure derived from [18]annulene, the dianion-based model has a four-fold symmetry, and was considered suitable for the description of metal complexes [23] (see Sect. 2.3.2). In yet another approach [24], based on the so-called perimeter model, the porphyrin macrocycle is derived from the [20]annulene dication (**1‴**). Both the [16]- and [20]annulene models were employed to describe electronic absorption spectra and magnetic circular dichroism of porphyrinoids [24, 25].

A general feature of all porphyrinoids is that their structures comprise a large conjugated ring (the macrocycle) that is composed of a number of smaller rings, usually five- or six-membered, that are linked either directly or through *meso* bridges. The small rings are derived from simple hetero- or carbocycles, which, when isolated from the macrocyclic frame, would often exhibit aromaticity of their own. In the following discussion, the term "macrocyclic aromaticity" will refer to the properties of the large ring, whereas the aromatic properties of the constituent small rings will be termed "local aromaticity." This distinction has no particular significance in regular porphyrins, but it becomes crucial for the description of certain porphyrinoids, such as benziporphyrins.

Let us consider a generalized structure **2** containing a smaller ring (cyclic subunit) incorporated into a large one (macrocycle), shown in Fig. 4. In this structure,

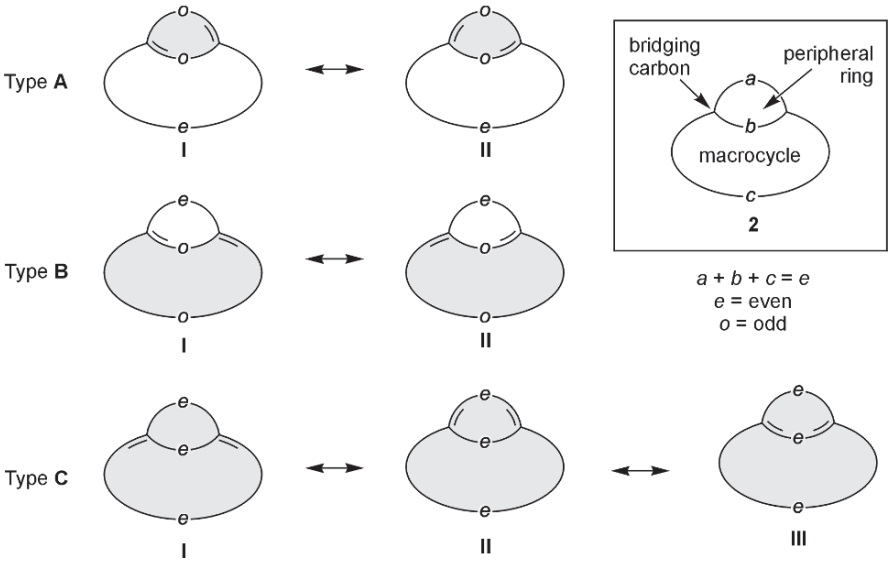


Fig. 4 Conjugation types in porphyrinoids. Fully conjugated circuits are *shaded*. For details, see text

which is assumed to have zero charge, three arcs denote π-conjugated chains (branches) consisting of a given number of carbon and other atoms (*a*, *b*, and *c*, respectively), each atom contributing one electron to the π system of the molecule. The two bridging carbons also participate in the conjugation and, consequently, any canonical structure of **2** must contain one double bond emanating from each bridgehead atom. The total π electron count of **2**, including the two bridgehead carbon atoms, is therefore $a + b + c + 2$, and it has to be an even number for a closed-shell structure. To meet this requirement, either all numbers *a*, *b*, and *c* must be even or exactly two of them must be odd. Depending on their relative parity, three conjugation types can be distinguished:

- Type **A** with *a*, *b* odd and *c* even corresponds to local conjugation. Here an [$a + b + 2$]annulene circuit can be distinguished, whereas no annulenoid circuits can be constructed involving the *c* branch.
- Type **B** described by *b*, *c* odd, *a* even (or, alternatively, *a*, *c* odd, *b* even) is characteristic of macrocyclic conjugation. An annulene circuit spanning the *b* and *c* branches (or *a* and *c*) is present, whereas the *a* branch (or *b*) is formally not conjugated with the rest of the molecule.
- Type **C** with *a*, *b*, *c* even represents combined local and macrocyclic conjugation. Three annulenoid pathways coexist, one for each pair of branches.

These three conjugation types may correspond to aromaticity or antiaromaticity, in accordance with the Hückel rule. They can be depicted using the partial resonance structures given in Fig. 4. An additional requirement is that each branch required to participate in cyclic conjugation not contain a formally two-electron heteroatom site (such as –NH–, –O–, etc.) or exocyclic double bonds (such as carbonyl groups). These structural elements are incompatible with Kekulé-type canonical structures. Finally, it should be noted that in the case of type **C** structures macrocyclic conjugation will be preserved, even when one of the *a* and *b* branches is not fully conjugated.

Conjugation type **B** is exemplified by the unprotonated pyrrole rings in free base porphyrin (Fig. 5). The N-protonated pyrroles represent a type **C** conjugation, from which the resonance contribution **C-III** is excluded (i.e., the *b* branch is not available for conjugation). Figure 6 gives further examples of subunit conjugation, which will be discussed in detail below. Type **A** conjugation is relevant in certain nonaromatic or partially aromatic systems described in this review, such as *m*-benziporphyrin (**147**, Sect. 4.1.1) or azuliporphyrin (**138**, Sect. 3.3.2). In this review, these macrocycles will also be called "cross-conjugated," to emphasize the absence of cyclic conjugation in the large ring. In type **B**-conjugated porphyrinoids, the macrocyclic pathway normally follows the "inner" edge of the cyclic subunit, though an example of "outer-type" conjugation is known. In some instances, type **B** conjugation can only be achieved in charge-separated structures, giving rise to weakly aromatic systems. Finally, type **C** normally occurs as its "outer half" variant, as described earlier for porphyrin, *p*-phenylene being the only subunit providing full **C** conjugation in porphyrinoids.

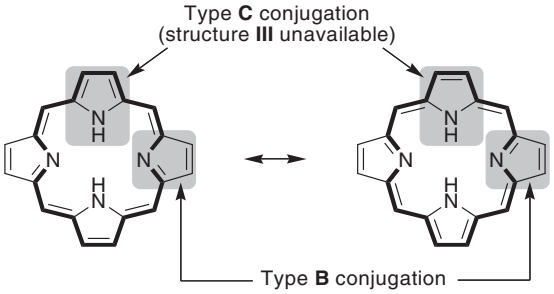


Fig. 5 Conjugation of pyrrole subunits in free base porphyrin (**1**)

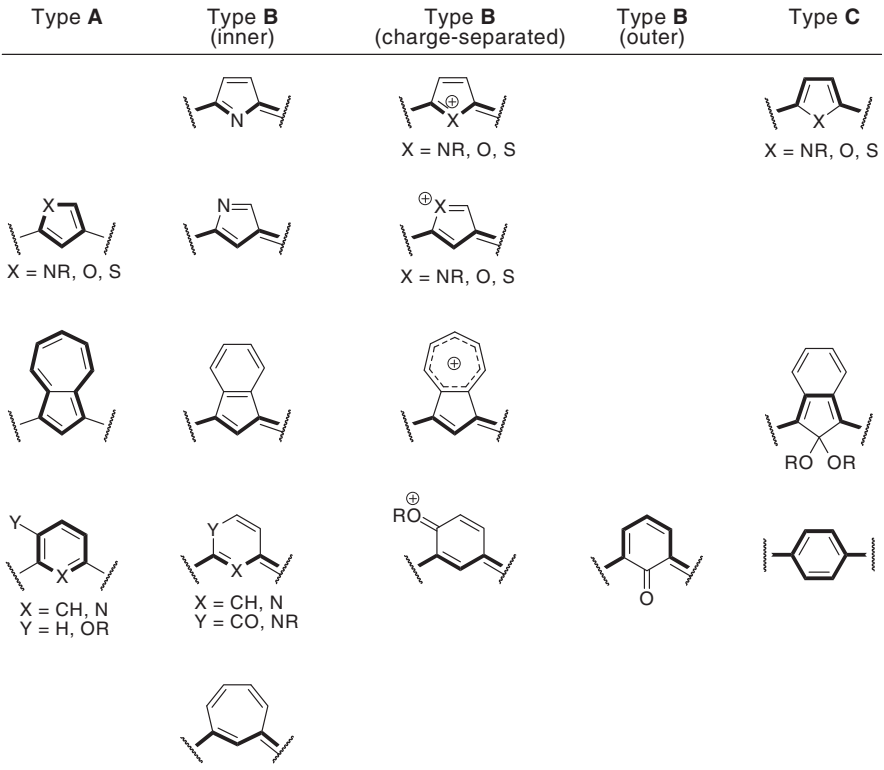


Fig. 6 Conjugation types feasible for various cyclic subunits

2.2 Porphyrins and Aromaticity Criteria

Aromaticity of π-electron systems is a complex phenomenon which is defined in terms of a variety of physical and chemical properties [26]. The following criteria are of particular value in porphyrinoid chemistry:

1. *Energetics*. Aromaticity is traditionally associated with additional energetic stabilization, and conversely, antiaromatic molecules have a higher energy than the corresponding polyenic reference compounds [27]. Stabilization energies of porphyrinoids, mostly derived from high level quantum chemical calculations [28], do not always correlate with the aromaticity perceived through ^{1}H NMR shifts. One major reason for this situation is that resonance energies per conjugated unit decrease with the increasing ring size [29], and in large macrocyclic structures they can be easily offset by conformational effects resulting from out-of-plane distortions or steric interactions. Furthermore, in large polycyclic systems, there may be a competition between different delocalization types, which are selectable by tautomeric equilibria. Examples of such situations are provided later in this review.
2. *Geometry*. Bond length equalization is a characteristic feature of aromatic porphyrinoids and can be used to identify preferred conjugation pathways in these molecules. Reliable bond lengths are available from high-level theoretical calculations, especially those employing the density functional theory [28], and from X-ray diffraction analyses. Unfortunately, the solid-state structures of porphyrinoids are frequently plagued with disorder, which usually results either from symmetry issues or prototropic tautomerism. Quantitative use of geometrical information is possible through geometry-based aromaticity indexes [30], of which HOMA [31] and HOSE [32], developed by the group of Krygowski, are the most popular.
3. *Magnetic criteria*. NMR shifts of protons attached to porphyrinoid rings are precise indicators of the aromatic character of these molecules, and are of particular value when comparisons can be made between structurally related systems [33]. The availability of protons located in the macrocyclic cores of many porphyrinoids is especially fortunate, as their shifts are much more sensitive to changes in the magnitude of the ring current. In general, in aromatic porphyrinoids signals of peripheral protons experience downfield shifts relative to their expected position in the absence of the ring current, whereas the inner protons are deshielded, and are often found at negative values of the δ scale. Accordingly, the difference $\Delta\delta = \delta_{outer} - \delta_{inner}$, calculated for signals with extreme downfield and upfield shift, is often taken as a semiquantitative measure of the ring current. In antiaromatic systems the shielding effect is reversed [34, 35], leading to negative $\Delta\delta$ values. Nucleus independent chemical shift (NICS) calculations [36, 37], as well as direct numerical simulations of ring currents [38] have also been employed for quantification of aromaticity in porphyrinoids.
4. *Electronic structure*. Electronic absorption spectra of regular porphyrins are characterized by the presence of a very strong absorption in the near UV-region (ca. 400 nm, $\log \varepsilon \sim 5$), known as the Soret band [39]. It is accompanied by a set of so-called Q bands of lower intensity, which appear in the visible region and are responsible for the distinct colors of porphyrins. The interpretation of electronic spectra of porphyrins is largely based on the classical four-orbital model developed by Gouterman [40]. The high ratio of absorption intensity in the Soret and Q regions (Soret:Q $\geq$ 10) has often been used as a rule-of-thumb indicator

of aromaticity, as it is much lower for systems with broken macrocyclic conjugation, such as phlorins or oxophlorins. Unfortunately, the Soret:Q ratio of porphyrin analogs, notably expanded porphyrins, is not as useful because it can be relatively small, even in systems that are unquestionably aromatic (such as cyclopyrroles, Sect. 2.5.2). Other optical methods, such as magnetic circular dichroism [24, 41] or two-photon absorption [42, 43], have been used to investigate the properties of porphyrinoid chromophores. Finally, HOMO–LUMO gaps, which are known to decrease with the increasing size of the conjugated system, can be obtained from electrochemical data.

2.3 Porphyrins and Chlorins

2.3.1 Prototropic Tautomerism and Acid–Base Chemistry

The correct structural formula of the porphyrin nucleus (**1**), first proposed by Küster in 1912, was proved synthetically by Fischer a few years later through a series of landmark syntheses [20]. It was immediately realized that Küster's formula might lead to two kinds of isomerism. The possibility of "resonance isomerism," resulting from different positions of double bonds, was excluded early [44]. The search for "N-isomerism," generated by different configurations of the pyrrolic NH protons (Fig. 7), proved more problematic. It was argued that stable N-isomers should yield identical acid salts and metal complexes, and no such effect had ever been observed for any two distinct free bases [44, 45]. Rothemund reported a separation of N-isomers of tetraphenylporphyrin (**1a**) [46] but his claims were later disproved [47] and the "isomer" was eventually identified as tetraphenylchlorin [48]. Eventually, on the basis of UV–vis and IR spectra, the "*trans*" structure (**1-1**) was proposed as the major tautomer of porphyrin, whereas contributions of the "*cis*" structure (**1-2**) and symmetrically hydrogen-bridged forms were excluded [49–51].

This interpretation was subsequently confirmed with a variety of other techniques including X-ray crystallography [52], solution and solid-state ^{n}H NMR spectroscopy (n = 1–3) [53–57], ^{13}C NMR [58], ^{15}N NMR [59], and laser induced fluorescence spectroscopy [60]. It was shown that the exchange between the *trans* tautomers is rapid at room temperature and proceeds with the intermediacy of the *cis* form. The tautomerization consists of consecutive single proton transfers, which have a substantial tunneling contribution. Using ab initio and DFT calculations, the relative energy of the *cis* tautomer was estimated as 7.6–8.1 kcal mol^{-1}, while the estimated barrier for *trans–cis* isomerization was ca. 14 kcal mol^{-1} (including the ZPVE correction) [61, 62].

As indicated in Fig. 7, the positions of the inner NH protons should affect the shape of the conjugation pathway. In particular, the C_β–C_β bonds in the N-unprotonated pyrrole rings should exhibit a stronger double-bond character than those in the N-protonated pyrroles. This structural effect was confirmed for the *trans* tautomer by X-ray analysis [63, 64] (for a more recently compiled database of X-ray

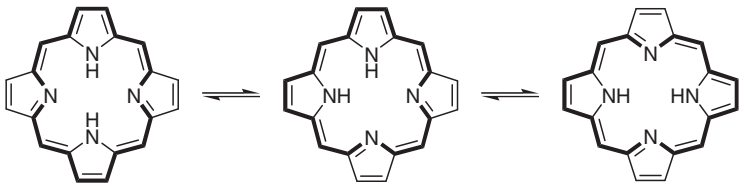


Fig. 7 Tautomerism in porphyrins

structural determinations of tetrapyrroles see [65]). It should, however, be noted that the C_β–C_β bonds in the porphyrin ring are generally shorter than the C_α–C_β distances, indicating that the delocalization pattern in the porphyrin ring is more complicated than implied by the [18]annulene model (see Sect. 2.3.2). Theoretical data obtained for both tautomers are also consistent with partial localization of the C_β–C_β bonds and show that the conjugation pathway is adjusted to positions of the inner NH protons [61, 62].

At room temperature the exchange between the equivalent *trans* tautomers **1-1** and **1-3** is rapid and the observed ^{1}H NMR spectrum of the porphyrin corresponds to an effective D_{4h} symmetry. By lowering the temperature, it is possible to slow the exchange process sufficiently to observe separate signals for the nonequivalent pyrrole rings. For tetraphenylporphyrin (**1a**) it was found that the β-H signals corresponding to the protonated and unprotonated pyrrole rings resonate respectively at 8.90 and 8.61 ppm [54]. This difference of chemical shifts is consistent with the conjugation pattern derived from [18]annulene (Fig. 3), as the deshielding effect should be weaker for the protons attached to the unconjugated C_β–C_β fragment.

A symmetrically substituted porphyrin possesses only one distinguishable *trans* tautomer (and only one possible *cis* tautomer). The number of distinguishable tautomers increases when the macrocycle is desymmetrized, usually by peripheral or internal substitution. Such structural modifications introduced to the porphyrin nucleus are often sufficient to create an energetic preference for one of the tautomers and, if tautomerization is still operative, for a particular transition state. An elegant example of this behavior was provided by a series of 2-substituted tetraphenylporphyrins that showed remarkable variations in the equilibrium between the two *trans* tautomers **3-R-1** and **3-R-2** (Fig. 8, R = substituent) [66]. It was subsequently shown by using saturation transfer experiments and lineshape analysis that the proton transfer in porphyrins bearing electron-donating substituents (**3-OMe** through **3-*i*-Pr**) is directional at temperatures below 200 K (the preferred direction of proton transfer is indicated with arrows in Fig. 8) [67]. A similar study was performed on deuteroporphyrin derivatives, providing further information on the relationship between peripheral substitution and internal tautomerism [68].

In chlorins (**4**), porphyrin derivatives with a reduced C_β–C_β bond, only one [18]annulene pathway is available, inducing a preference for the corresponding *trans* tautomer (**4-1**, Fig. 9). The tautomerism of chlorins was studied using NMR

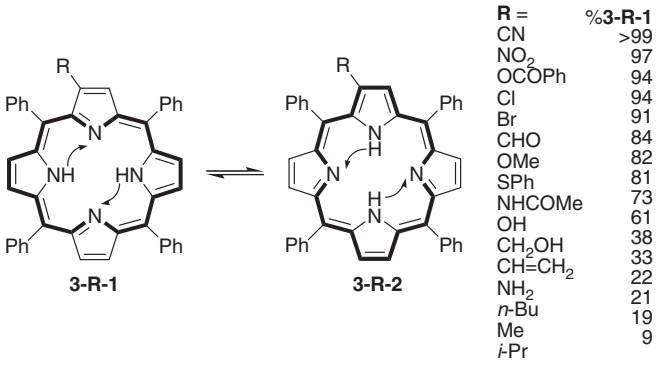


Fig. 8 Dependence of the equilibrium between the *trans* tautomers in a series of 2-substituted tetraphenylporphyrins (**3-R**). *Arrows* indicate the preferred direction of proton transfer. Data cited after [66]

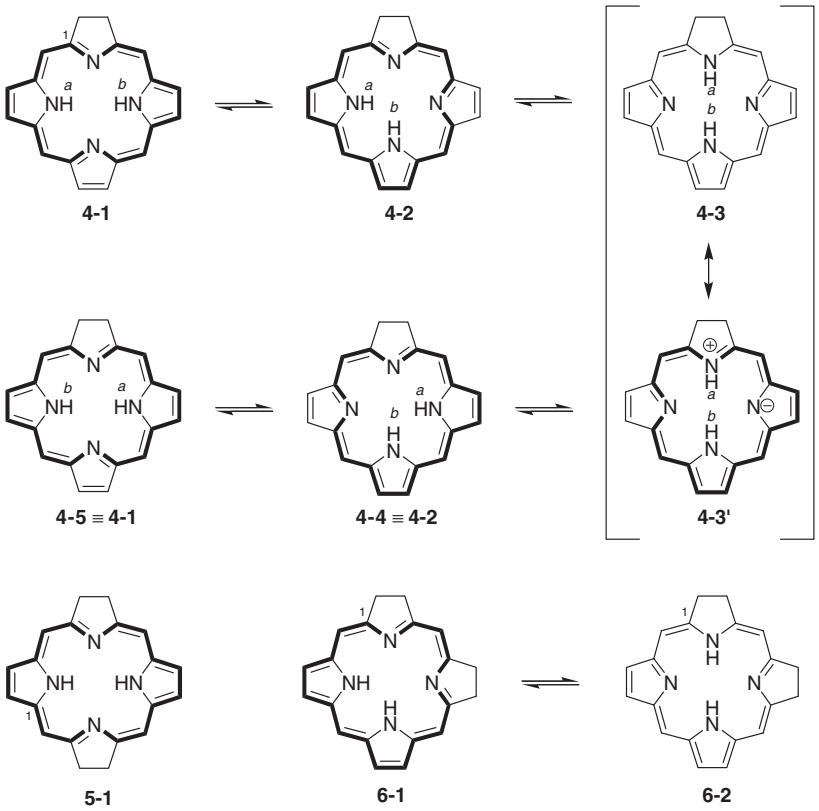


Fig. 9 Tautomerism in chlorins (**4**), bacteriochlorins (**5**), and isobacteriochlorins (**6**)

spectroscopy for a number of synthetic and naturally occurring systems [54, 69–72]. In each case, tautomer **4-1** was observed as the dominant form in solution, but there was also evidence that species **4-3**, in which macrocyclic conjugation is interrupted, might be present at measurable concentrations at higher temperatures [71]. Furthermore, it was found that the activation energy for the transposition of the inner NH protons (exchange between **4-1** and **4-5**) is generally higher in chlorins than in the corresponding porphyrins, and the exchange is slow at room temperature. On the basis of spectroscopic data and semiempirical calculations, it was proposed that the dominant exchange pathway from **4-1** to **4-5** involves two fully conjugated *cis* tautomers (**4-2** and **4-4**) and the nonconjugated *trans* tautomer **4-3**. The latter species, destabilized by incomplete macrocyclic conjugation, is deemed responsible for the high activation barrier for the tautomerization. **4-3** can however be expected to exhibit some macrocyclic aromaticity through the inclusion of charge-separated canonical structures, such as **4-3´**.

Bacteriochlorins, in which two opposite pyrrole rings are reduced at the β positions, exist as the tautomer **5-1** (Fig. 9). The barrier to tautomerization is even higher than in the chlorins and the exchange, observed by NMR, is slow even at elevated temperatures [69]. This is not surprising because the intermediate *trans* tautomer, bearing NH protons on the reduced rings is nonaromatic, and requires double charge separation to achieve a conjugated [18]annulenoid circuit. For isobacteriochlorins, the two tautomers **6-1** and **6-2** are of comparable energy [73] and can be detected spectroscopically [69, 74–76]. It is worth noting that the macrocyclic ring current (perceived through the chemical shifts of the inner NHs) diminishes in the sequence: porphyrins, chlorins, isobacteriochlorins [74]. This effect was attributed to peripheral reduction but it might also result from the presence of the less aromatic tautomers (such as **4-3** or **6-2**) in the fast exchange limit. Similar tautomerization effects were recently considered for porphyrin di- and tetraones in conjunction with their redox chemistry [77].

When functionalities containing labile protons, such as OH and NH_2 groups, are introduced on the periphery of the porphyrin macrocycle, they may participate in the overall tautomerism of the molecule, expanding the number of available protonation states. *meso*-Hydroxylated porphyrins exist solely in the keto form (e.g., **7a**, Fig. 10), known as oxophlorin, with interrupted macrocyclic conjugation [78]. The first protonation step in oxophlorins occurs on the free nitrogen site, resulting in a monocation (**8a**) that is also nonaromatic. Upon addition of the second proton, which attaches to the peripheral oxygen, a *meso*-hydroxyporphyrin dication **9a-1** is formed, which regains macrocyclic aromaticity (an alternative dication **9a-2** was proposed as a transient species, in which the second proton attaches to the *meso* position 15). The same effect can be achieved by coordination of divalent metal ions, which form aromatic *meso*-hydroxyporphyrin complexes of the general structure **10** [78]. Alternatively, the tautomeric preferences of oxophlorins can be altered by an appropriate placement of a hydrogen bond acceptor in the vicinity of the 5-oxo group, as in compound **11**, which was found to exist as the hydroxyporphyrin tautomer stabilized by an intramolecular hydrogen bond with the adjacent 3-oxo functionality [79]. In the case of *meso*-aminoporphyrins (structure **12-1**, Fig. 10),

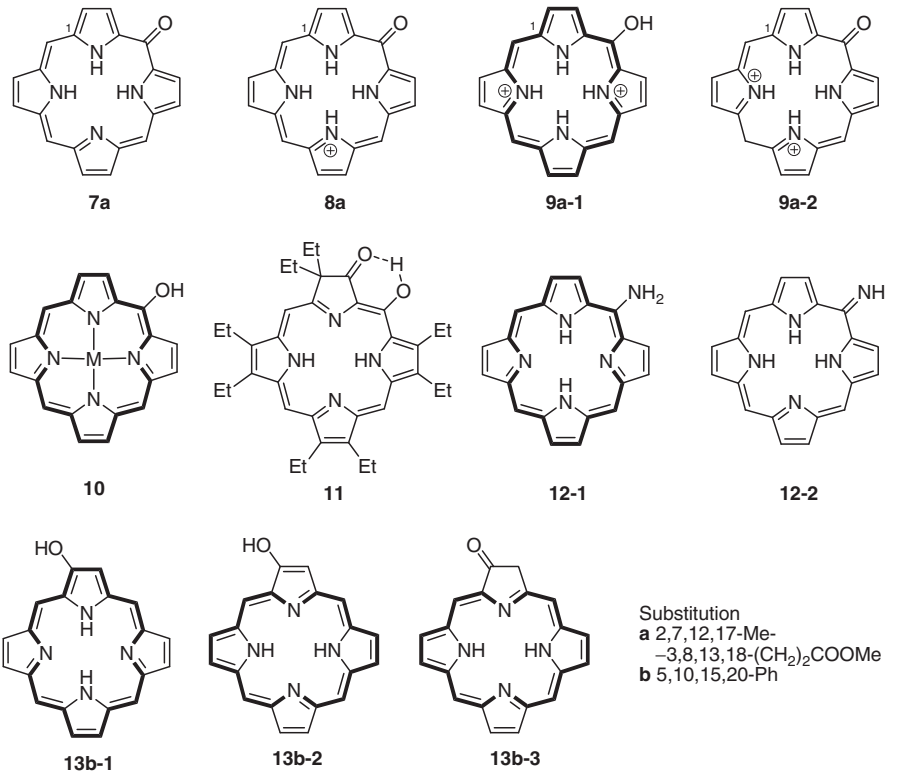


Fig. 10 Tautomerism in oxophlorins (**7**–**11**), *meso*-aminoporphyrins (**12**), and β-hydroxyporphyrins (**13**)

the corresponding imino tautomers **12-2** are normally observed and in some cases become the predominant species in solution [80, 81].

In the case of β-substituted 2-hydroxy-5,10,15,20-tetraphenylporphyrin, an equilibrium was detected in solution, which involved three tautomers: aromatic hydroxy (**13b-1**), enol (**13b-2**), and keto (**13b-3**, Fig. 10) [82]. For a sample of this compound with all exchangeable protons replaced with deuterons, the ratio of the three species **13b-1**:**13b-2**:**13b-3** obtained from integration of a ^{1}H NMR spectrum recorded at 220 K was 2:3:5. In contrast, for the 2-amino derivative **3-NH$_2$** (Fig. 8), no imino tautomers analogous to **13b-3** were detected [66].

Fixation of aromaticity pathways in porphyrins can also be achieved through internal substitution. In the X-ray structure of *N*-methylporphyrin **14** (Fig. 11), the NH proton was localized on the nitrogen opposite the internal alkyl group, leading to an appropriate adjustment of the conjugation pathway [83]. A complementary example is provided by octaethylporphyrin *N*-oxide **15**, which exists as the 22*H*,24*H* tautomer both in solution and in the solid state [84].

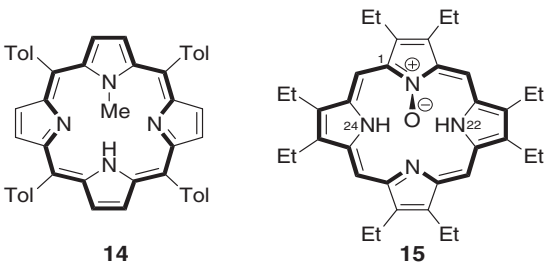


Fig. 11 Localization of conjugation pathways in porphyrins by means of internal substitution

2.3.2 Metal Coordination

Coordination of metal ions often has a dramatic effect on the π delocalization in porphyrins and porphyrinoids. It has particularly conspicuous influence on the electronic spectra of metalloporphyrins, which show a dependence on the identity of the metal ion, axial ligation, oxidation level, and spin state. In regular porphyrins, metal coordination reduces the number of observed Q bands from four to two, reflecting the higher symmetry of the chromophore relative to the free base. However, detailed quantitative information on the π-electron delocalization is more easily accessible from other physical methods.

Early X-ray structural determinations revealed that the bond length pattern of the porphyrin ring undergoes consistent changes upon coordination of metal ions [23, 64]. In particular, the effective symmetry of the macrocycle increases to D_{4h}, making all the pyrrole rings equivalent. Nevertheless, the observed C_β–C_β and C_α–C_β bond lengths are not consistent with either of the fully symmetric delocalization patterns (**1″** and **1‴**, Fig. 3). In the case of the [16]annulene model, proposed in an early quantum mechanical study [85], one would expect perfect fixation of C_β–C_β double bonds, whereas the [20]annulene delocalization should lead to effective equalization of the C_β–C_β and C_α–C_β distances. Actual (averaged) X-ray structural data show only partial fixation of the C_β–C_β bonds in metalloporphyrins. It was therefore suggested that the delocalization pattern in metal complexes is more appropriately described as a combination of six [18]annulenoid pathways formally derived from the different *trans* and *cis* tautomers of the free base (Fig. 12) [86]. Further support for this depiction of aromaticity was gained from measurements of allylic $^4J_{HH}$ coupling constants observed in the ^{1}H NMR spectra of a variety of β-methyl porphyrins and their metal complexes [86]. In agreement with the structural data, it was found that the degree of C_β–C_β bond fixation in metalloporphyrins, while smaller than in the unprotonated pyrrole rings of corresponding free bases, is not compatible with the [16]annulene delocalization.

In a more recent study, the problem of π delocalization in porphyrins and metalloporphyrins was reinvestigated using two different aromaticity indexes, HOMA and NICS [37]. The harmonic oscillator model of aromaticity (HOMA) [31] quantifies the aromaticity of a system on the basis of the calculated deviation of its

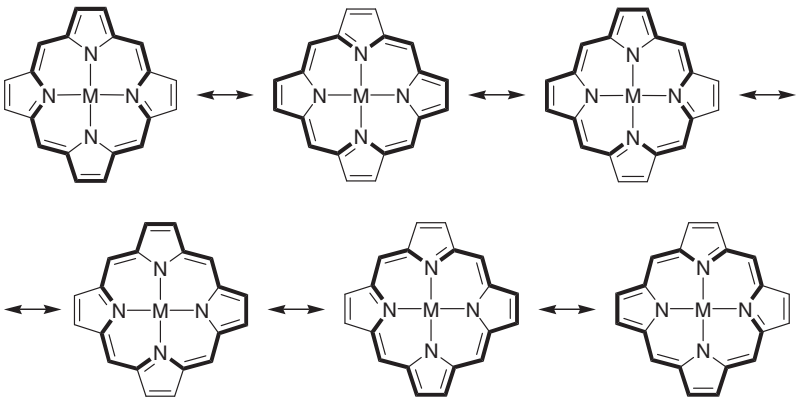


Fig. 12 Possible resonance contributors to the π delocalization in metalloporphyrins (after [86])

bonding pattern from that corresponding to perfect delocalization. HOMA, which can use either experimental or theoretical bond lengths, is normalized to yield the value of zero for a completely localized system and 1 in the case of perfect (benzene-like) delocalization. The nucleus-independent chemical shifts (NICS) [36] are defined as NMR shifts calculated at centers of rings. A strongly negative value typically corresponds to aromaticity (diatropicity), whereas positive values are indicative of the antiaromatic (paratropic) character of the ring. The picture of porphyrin aromaticity obtained from HOMA and NICS data was essentially consistent with previous analyses discussed above (Fig. 13). Additionally, it was found that the N-protonated pyrrole rings in free bases retain much of the aromaticity of the isolated pyrrole and that the protonated nitrogens are significantly involved in π-delocalization (i.e., they are conjugated with the [18]annulenoid substructure). In contrast, the aromaticity of the unprotonated pyrroles is significantly diminished, and their C_β–C_β bonds are largely localized. The properties of pyrrole rings in metalloporphyrins are intermediate between the two different types observed in free bases. Interestingly, while the C_β–C_β bonds in metalloporphyrin structures are conjugated with the macrocyclic frame, they were found to be localized in the calculated structure of the porphyrin dianion. Such an anion is therefore appropriately described in terms of the [16]annulene model **1″** [37].

2.3.3 Redox Chemistry

Oxidation and reduction of all-carbon annulenes are known to result in cationic or anionic species with aromatic properties different from those of the neutral ring, offering a textbook example of the validity of Hückel rules [87]. In pyrrole-containing porphyrinoids, such oxidations and reductions can be realized with retention of charge neutrality because the charge can be adjusted by protonation or

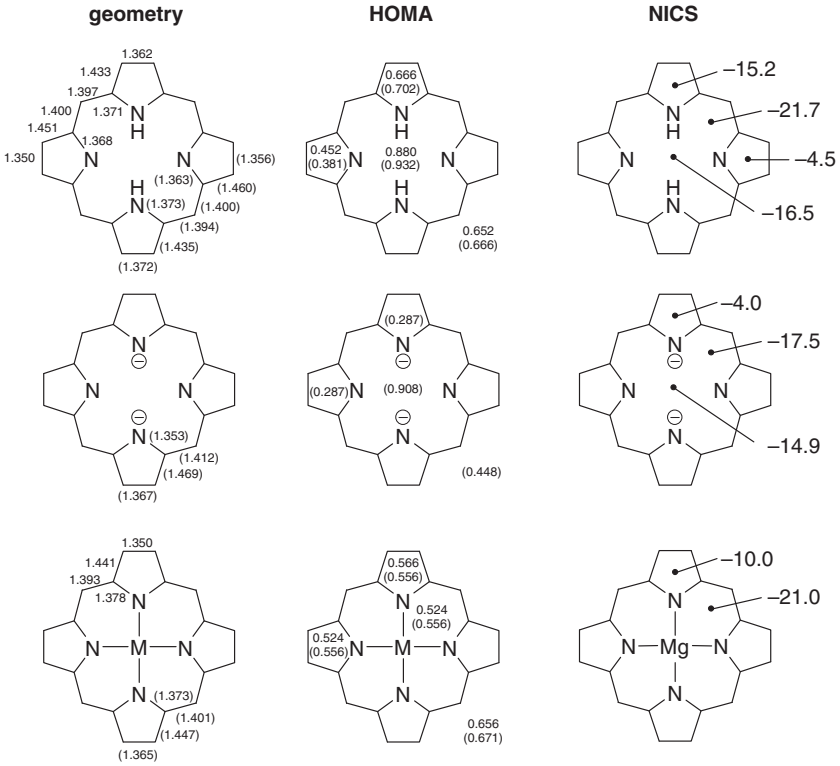


Fig. 13 Aromaticity analysis in free-base porphyrin (*top*), porphyrin dianion, and porphyrin complex (*bottom*) [37]. Bond lengths (in Ångstroms) are averages obtained from X-ray structural data. Values in *parentheses* correspond to calculated geometries (B3LYP/6-31G*, no substituents, M = Mg). HOMA indices were calculated from the average (calculated) bond lengths. The values *inside* the macrocyclic ring and *outside* the macrocycle correspond respectively to the "inner cross" ([16]annulene circuit) and the complete macrocycle. NICS values (GIAO-RHF/6-31 + G*) were calculated at the points indicated with *dots*

deprotonation of the pyrrolic nitrogens (Fig. 14). This feature is useful because neutral porphyrinoids can be less reactive and easier to investigate than annulene ions of similar ring size. It is possible to envisage two additional systems, [16]porphyrin (dehydroporphyrin, **16**, Fig. 14) and [20]porphyrin (dihydroporphyrin, isophlorin, **18**), that are respectively an oxidized and reduced version of the parent macrocycle **1**. These two structures are antiaromatic according to the Hückel rule, and are thus expected to be less stable than [18]porphyrin. An additional difficulty in stabilizing [20]porphyrins results from the existence of isomeric structures with interrupted conjugation, such as phlorin (**19**) and porphodimethene (**20**), which may form as alternative products during the reductive syntheses of **18**. Conversely, competitive formation of isoporphyrins (**17**) was never observed in porphyrin syntheses, even though substituted isoporphyrin derivatives are known [88–90].

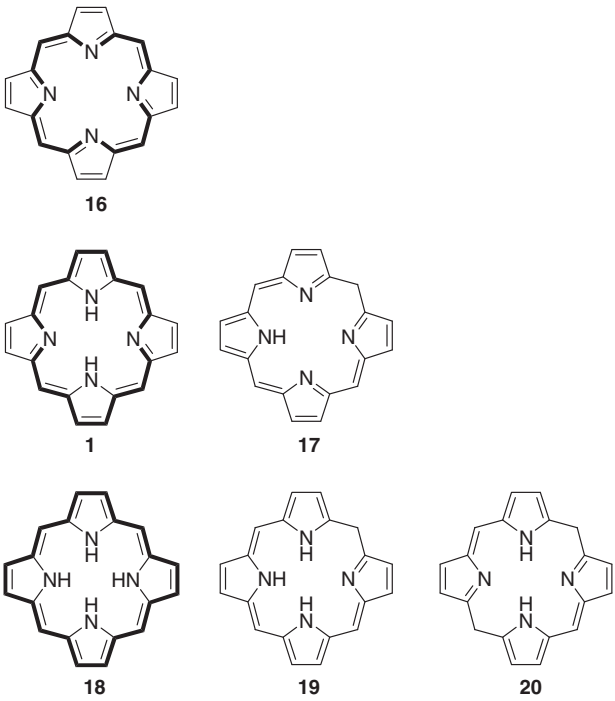


Fig. 14 Oxidation states of porphyrin

Apparently, the first examples of [16]annulenoid porphyrin derivatives were obtained by Eschenmoser and coworkers during their work on corphin (**21**, Fig. 15), a peripherally reduced porphyrin derivative [91]. Free base corphin has the appropriate oxidation level to adopt a tetraaza[16]annulene structure, but it actually exists as the cross-conjugated tautomer **21**. However, some of the complexes of corphin with divalent metals (such as Zn or Pd) were shown to have the symmetrical structure **22**, and their ^{1}H NMR spectra revealed a modest paratropic ring current, comparable with that of [16]annulene [92–94].

The first derivatives of [16]porphyrin have been obtained only recently. The highly substituted compound **16a** was obtained serendipitously by oxidizing the lithium salt of the corresponding [18]porphyrin with thionyl chloride. In the solid state, the molecule of **16a** is even more nonplanar than the substrate (with the RMS deviation from the mean plane of 0.836 Å) and exhibits an unusually strong alternation of bond lengths, characteristic of antiaromatic structures [95]. The electronic spectrum of **16a** is characterized by a strongly blue-shifted Soret band (339 nm) and the absence of Q bands in the visible region. However, the presence of a paratropic ring current cannot be judged from the ^{1}H NMR data provided. The stability of **16a**, which gradually decomposes in solution, can be improved by increasing the steric congestion around the macrocycle (as in **16b**).

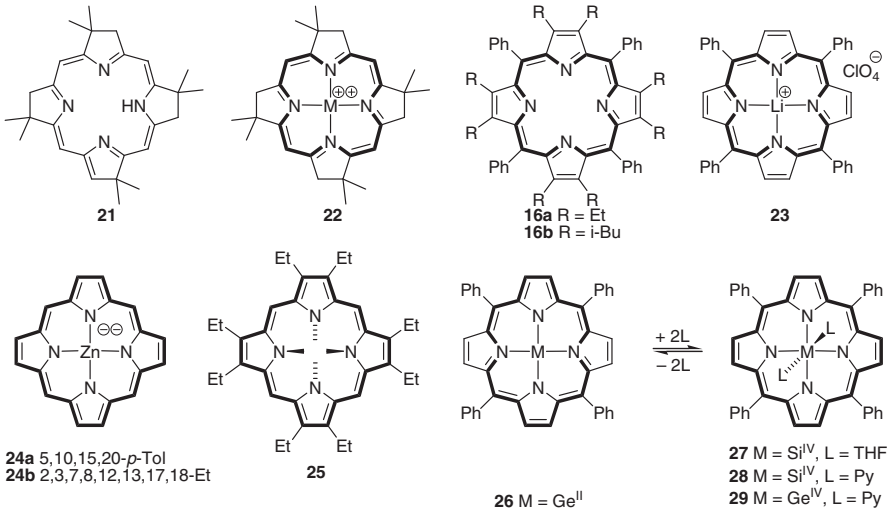


Fig. 15 Examples of [16]- and [20]porphyrins

Apparently, [16]porphyrins **16a** and **16b** are stabilized by the presence of large peripheral substituents and by the resulting out-of-plane distortion of the macrocycle. It was found, in a different study, that the dehydroporphyrin macrocycle can also be stabilized through metal coordination [96]. Compound **23**, obtained via chemical oxidation of dilithium tetraphenyl[18]porphyrin, is stable in CH_2Cl_2 solution in the presence of air, and is only slowly decomposed by water. In CH_3CN solution, it undergoes slow reduction to the Li(TPP) radical. In analogy to **16a–b**, **23** exhibits significant bond length alternation and strong out-of-plane distortion, even though the periphery of the macrocycle is not sterically crowded. Paratropicity of **23** was deduced from the ^{1}H NMR data and was further confirmed by NICS calculations.

The first example of a [20]porphyrin structure was provided by the dianions of zinc porphyrins **24a–b**, obtained by reduction with metals [97]. These systems showed very significant paratropic ring currents, for instance the *meso* protons of **24b** resonated at –3.9 ppm. The first neutral [20]porphyrin, *N*,*N*,*N*,*N*-tetramethyloctaethylisophlorin **25**, was obtained by reduction of the *N*,*N*,*N*,*N*-tetramethyloctaethylporphyrin dication with sodium anthracenide [98]. Compound **25** has a nonplanar structure with the inner methyl groups alternating above and below the macrocyclic plane. In the solid state, double bonds are localized along the [20]annulene pathway. In solution, however, **25** undergoes a degenerate π-bond shift that is fast at room temperature. At –72 °C, the process is sufficiently slow to yield a ^{1}H NMR spectrum corresponding to the bond-localized structure. **25** is easily reoxidized to the dication and reacts with trifluoroacetic acid to yield a *meso*-protonated phlorin cation.

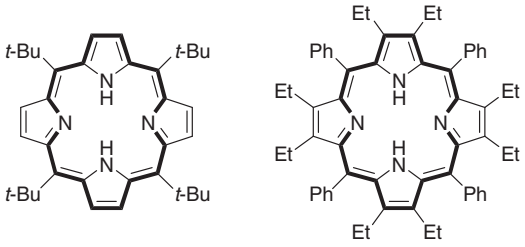
[20]porphyrin complexes were obtained with tetravalent ions Si(IV) (**27** and **28**) and Ge(IV) (**29**) bearing appropriate axial ligands [99, 100]. The latter system is reversibly formed from a Ge(II) [18]porphyrin complex **26** upon addition of pyridine ligands. Systems **27**–**29** are paratropic and show remarkable downfield shifts for the signals of axial ligands. Bond localization is evident from the X-ray structures, but π-bond shifts are apparently very fast in solution even at very low temperatures. An extremely unstable diboranyl [20]porphyrin, containing an in-plane coordinated B^{II}–B^{II} unit, was obtained by chemical reduction of an appropriate diboranyl porphyrin precursor [101].

Interestingly, radical porphyrin derivatives with oxidation states intermediate between those of [16]-, [18]- and [20]porphyrin are known. In particular, neutral complexes of tetraarylporphyrins with lithium [102] and aluminum [103] were obtained and characterized in the solid state. These complexes of main-group metals are of interest, because the oxidation state of the metal ion is in each case well defined.

2.3.4 Peripheral Substitution

As shown above, there are two complementary substitution patterns typically employed in synthetic porphyrins: *meso*-aryl substitution, which leaves unsubstituted β positions, and β-alkyl substitution, wherein the *meso* positions are free. By introduction of bulky substituents (as in **1c**) or simultaneous substitution of *meso* and β positions (as in **1d**) it is possible to introduce steric congestion on the periphery, which results in a significant distortion of the macrocycle (Fig. 16) [104]. The latter strategy is effective because of the small distance between adjacent *meso* and β substituents in porphyrins, a fact appreciated by R.B. Woodward during his work on the synthesis of chlorophyll [105]. The out-of-plane distortions of the porphyrin ring have been classified into several distinct types that differ in the relative displacements of pyrrole rings and *meso* carbons. In general, distortions of the macrocycle, both in and out of plane, are amenable to quantitative treatment using normal-coordinate decomposition [106–109].

The deformation of the π-system of the porphyrin ring affects its chemical reactivity and various physical properties. Highly substituted systems are more susceptible



1c **1d**

Fig. 16 Heavily substituted porphyrins

to *meso*-addition reactions [110] and subsequent formation of nonaromatic systems containing tetrahedral *meso* carbons, such as phlorins or porphodimethenes. In these systems the peripheral strain is relieved by placing the saturated *meso* bridge above the macrocyclic plane [104]. Other reactions, such as electrophilic dealkylation [111], also proceed efficiently in distorted porphyrins. All these observations indicate that aromatic stabilization in such systems is partially outweighed by steric repulsions, which results in enhanced reactivity.

The destabilization of the π system caused by out-of-plane distortion leads to a smaller HOMO–LUMO gap and, consequently, to red shifts of electronic absorptions. For instance the positions of the Soret and Q_0 bands are respectively 417 and 659 nm in **1c** and 446 and 691 nm in 5,10,15,20-tetra-*n*-butylporphyrin [110]. Interestingly, the reduction of the diatropic ring current caused by distortion is only moderate [33].

2.4 Porphyrin Isomers

In regular porphyrins, the four pyrrole rings alternate with *meso* bridges in a cyclic structure, yielding a skeleton with fourfold symmetry. By changing this sequence of subunits, seven additional structures can be constructed, known collectively as porphyrin isomers (Fig. 17) [4]. Elaboration of these macrocyclic motifs, pioneered by the group of E. Vogel, required considerable synthetic effort and ingenuity and had a lasting impact on porphyrinoid chemistry [4, 113]. To date, four isomers: porphycene **30**, hemiporphycene **31**, corrphycene **32**, and isoporphycene **33** have been synthesized. Aromatic properties of these and related systems are discussed below.

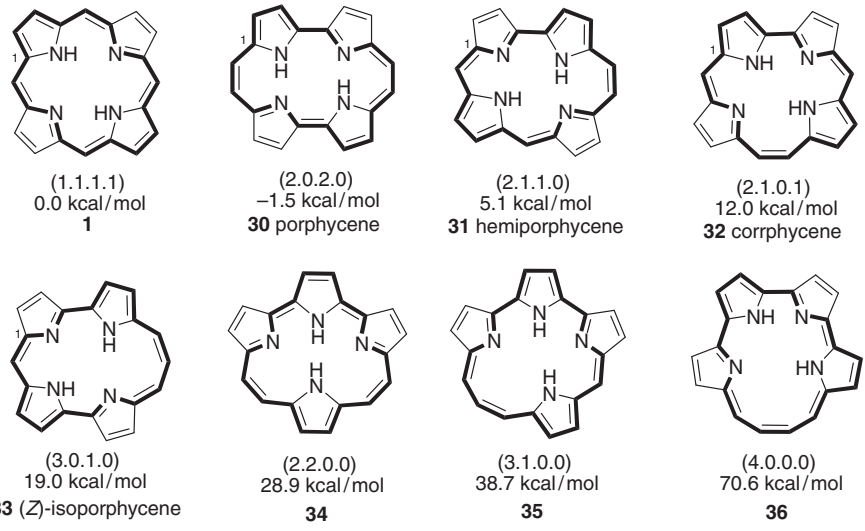


Fig. 17 Porphyrin isomers. Relative energies obtained from DFT calculations (BLYP/6-31G**// BLYP/3-21G) are taken from [112]

2.4.1 Porphycene

Porphycene, or [18]porphyrin(2.0.2.0), was the first porphyrin isomer synthesized [114] and has been the subject of extensive experimental and theoretical research. Porphycenes are available in several substitution variants (including the original unsubstituted macrocycle **30a**, Fig. 18), and have been transformed into a number of metal complexes [4]. Peripheral substitution provides a means of fine-tuning the properties of the macrocycle, both through electronic and steric effects. The steric factor, which affects both the complexing capabilities of porphycenes and the strength of intramolecular hydrogen bonding, is explained in Fig. 19 [115]. The four nitrogen atoms in sterically unstrained porphycenes form a rectangular core elongated along the axis parallel to the bipyrrolic subunits. For instance, it has dimensions of 2.83 and 2.63 Å in the unsubstituted **30a** [114]. Introduction of *meso* substituents (9,10,19,20) induces further elongation of the N_4 rectangle, which has

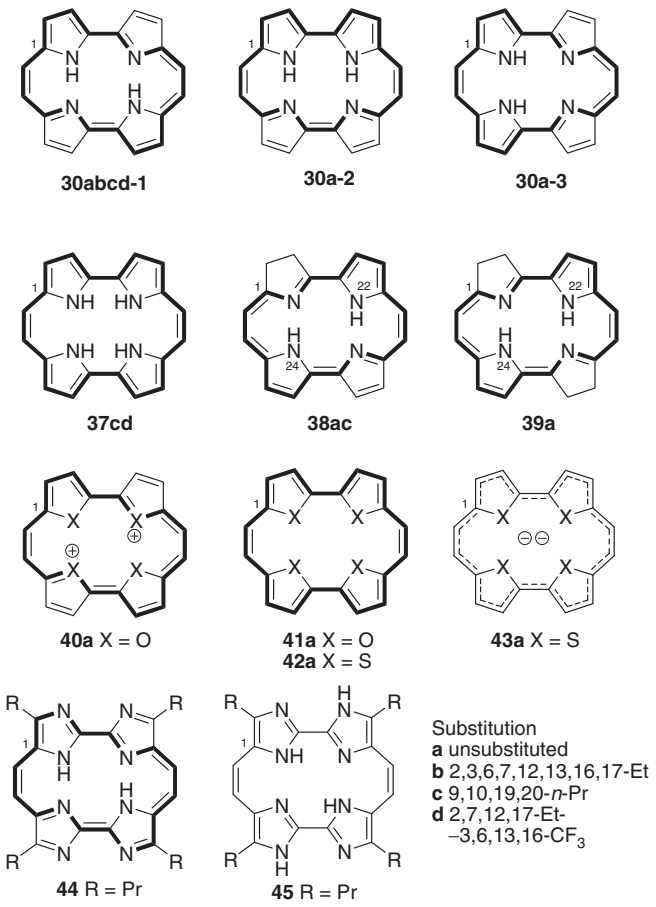


Fig. 18 Porphycenes and related molecules

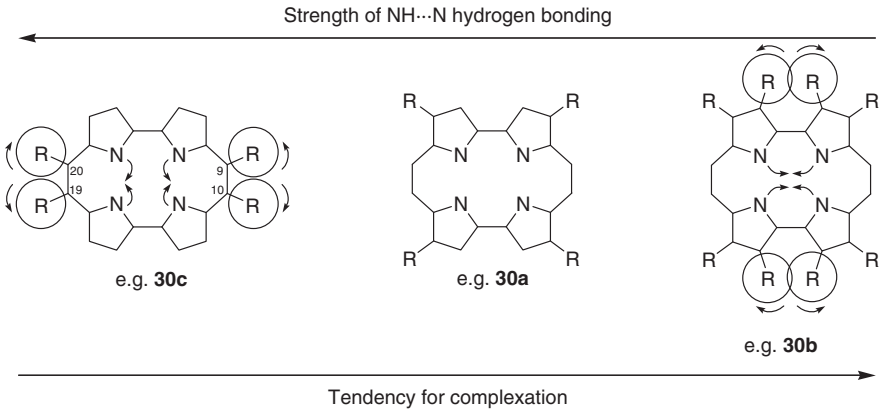


Fig. 19 Steric effects in differently substituted porphycenes (based on [115])

the dimensions of 2.90 and 2.53 Å in **30c** [115]. In porphycenes bearing substituents at positions 3,6,13,16 the macrocyclic core is deformed in the opposite direction (i.e., towards a square porphyrin-like geometry) resulting in a nearly equilateral N_4 rectangle, slightly elongated parallel to *meso–meso* bonds (2.73 and 2.80 Å in **30b** [116]). The square-shaped macrocyclic core improves the stability of metal complexes, making **30b** and related porphycenes suitable for coordination chemistry research.

Porphycenes were synthesized with the aim of testing the porphyrin–annulene analogy and, in line with expectations, were shown to possess porphyrin-like aromaticity. Their ^{1}H NMR spectra displayed downfield shifts of peripheral protons, which indicated a diatropic ring current. Interestingly, the signals of inner NH protons appeared at moderately high field, not reaching the negative shift values typical of regular porphyrins. This difference was explained as an effect of intramolecular hydrogen bonding and, in fact, the NH shifts correlated with the H-bonding strength inferred from structural data. For instance, the NH signals in **30b**, **30a**, and **30c** resonate at 0.65, 3.15, and 6.82 ppm, respectively. In agreement with the predictions of the perimeter model [24], electronic spectra of porphycenes are qualitatively similar to those of porphyrins, exhibiting separate Soret and Q regions, as well as similar extinction coefficients. The Q bands are shifted to shorter wavelengths resulting in the distinctive blue color of porphycenes. However, in contrast to porphyrins, which are typical soft chromophores in magnetic circular dichroism (MCD), the porphycene chromophore was found to be relatively insensitive to structural changes and was characterized as negative-hard [117].

Prototropic tautomerism in porphycenes exhibits characteristics that are vastly different from the behavior of regular porphyrins and has therefore been researched using a variety of techniques, including high-level electronic spectroscopy methods [41]. Initial ^{15}N CPMAS NMR experiments carried out on **30a** revealed that proton

scrambling was much faster than in porphine and remained extremely rapid even at 107 K, making it impossible to measure rate constants and to identify the actual tautomers involved [118]. Available X-ray data, marred with positional disorder, were also not helpful in determining the tautomeric preferences of porphycene. Theoretical calculations predicted the *trans* tautomer of porphycene **30a-1** to be more stable than the *cis* form **30a-2** by 4–8 kcal mol^{-1} [119]. The other *cis* form **30a-3** is even higher in energy, presumably because of strain and disruption of hydrogen bonding. A combination of spectroscopic methods, including fluorescence anisotropy measurements, fluorescence excitation in electronic jets, and single-molecule fluorescence were systematically used to explore ground- and excited-state tautomerism of porphycenes [41, 120–125]. For all systems studied, the *trans* tautomer **30-1** was found to dominate under various conditions. The *cis* species **30-2** was only observed in *meso*-substituted porphycenes such as **30c**, presumably as a consequence of the extremely strong hydrogen bonds in these species. In all cases, tautomerization proceeded via synchronous double hydrogen tunneling gated by a low frequency vibrational mode. Consequently, the associated activation barrier for proton transfer can be as low as ca. 0.6 kcal mol^{-1}. It is lowered with the increase in the hydrogen bonding strength and thus becomes higher in the excited singlet states, in which the relevant NH···N separations are larger than in the ground state.

Three reduced forms of porphycene are known: 21,23-dihydro (**37**), 2,3-dihydro (**38**), and 2,3,12,13-tetrahydro (**39**), which are analogous, respectively, to the porphyrin-derived chlorin (**4**), isophlorin (**18**), and bacteriochlorin (**5**) [126, 127]. The isophlorin-like form **37c**, termed pyrrolophanediene, is of particular interest because it is completely nonplanar and, in spite of its formal 20-π electron circuit, shows no signs of paratropicity [127]. Interestingly, a β-substituted derivative **37d** was recently obtained, which is also polyenic, even though its ruffled conformation could potentially permit sufficient π-orbital overlap to result in paratropicity [128]. The chlorin-like structure **38**, which is diatropic as expected, exhibits two NH signals in the room temperature ^{1}H NMR spectrum corresponding to 22-H (6.45 ppm in **38a**) and 24-H (3.51 ppm), which again indicate strong hydrogen bonding [126]. **38** is apparently thermodynamically more stable than **37**, as can be judged from **37c** being converted to **38c** under acid catalysis.

A number of heteroporphycenes have been synthesized containing various heterocyclic units such as furan [129], thiophene [130, 131], or imidazole [132]. Two oxidation levels were observed for tetraoxaporphycene: the diatropic 18-π electron dication **40a** and 20-π electron neutral species **41a** [129]. Unlike compound **37c**, **41a** adopted a planar conformation and exhibited a moderate paratropic ring current in the ^{1}H NMR spectrum. Interestingly, the analogous [20]tetrathiaporphycene **42a** is highly distorted from planarity and could not be oxidized to the respective dication [130, 131]. However, chemical reduction of **42a** yielded a weakly diatropic 22-π electron dianion **43a**. Electrochemical data show that, similarly to porphyrins, porphycenes and their complexes exhibit multiple oxidation and reduction events associated with the π-electron system, which are significantly affected by peripheral substitution and ring fusion [133–135]. Similar investigations were also carried out for other porphyrin isomers and related systems (e.g., [135–138]).

A redox couple similar to that of tetraoxaporphycene was also found in "imidacene," (**44**) a tetraimidazole analog of porphycene [132]. **44** exhibits macrocyclic aromaticity similar to porphycenes, but has limited chemical stability. Its reduced analog, "dihydroimidacene" **45** is a stable compound, and is only slowly oxidized to **44** by oxygen. **45** can in principle have a number of distinct tautomers, but it was assumed that two of the mobile protons are bound on the periphery while the other two reside in the core, thus preserving the intramolecular hydrogen bonding pattern typical of porphycenes. Such a structure is cross conjugated and is therefore consistent with the absence of a macrocyclic ring current in **45**. Unfortunately, neither spectroscopic nor theoretical methods were used to explore proton transfer equilibria of this interesting compound.

2.4.2 Other Isomers

The calculated energies of unsubstituted porphyrin isomers relative to regular porphyrin are given in Fig. 17 [112] (for a more extensive set of data see [139]). In each case the most stable tautomer of the all-(*Z*) configurational isomer was chosen. The relative energies span a range of ca. 70 kcal mol^{-1}, porphyrin and porphycene being the most stable structures. Interestingly, the energy of porphycene is slightly lower than that obtained for porphyrin, which likely reflects the stabilizing effect of strong hydrogen bonding [112]. Other systems, especially those possessing longer sequences of *meso* carbons, such as **35** and **36**, are predicted to be destabilized, presumably because of increased angular and torsional strain. It should be noted that the porphyrin isomers, which share the same oxidation level, are all predicted to possess an aromatic, [18]annulenoid circuit. These predictions have been verified experimentally for three systems: corrphycene **32** [140], isoporphycene **33** [141], and hemiporphycene **31** [142–144], all of which are indeed aromatic.

Octaethylcorrphycene exists in solution as the *trans*-protonated tautomer **32a-1** shown in Fig. 20. Unexpectedly, in the solid state, the presence of the *cis* tautomer **32a-2** (21*H*,22*H*) was revealed by X-ray diffraction analysis. Rates of tautomerism determined for **32a** in solution using dynamic NMR spectroscopy are higher than those in porphyrins but slower than in the case of porphycenes, indicating an intermediate strength of intramolecular hydrogen bonding. The $\Delta G^{\ddagger}$ for this process was estimated as 8.3 kcal mol^{-1}.

Isoporphycene **33** possesses a sequence of three consecutive *meso* bridges, in which *cis–trans* isomerism might occur. In fact, two isomers **33a-1** and **33a-2** (labeled *Z* and *E*, respectively) were observed for the octaethyl derivative (Fig. 20) [141]. The two species were isolated as a mixture containing 98% of **33a-2** and 2% of **33a-1**, which could not be separated, indicating a relatively fast interconversion between the isomers. Both species were distinctly diatropic, and as expected the 15-H proton showed a dramatic difference of its chemical shift between **33a-2** and **33a-1**. Tautomerism in isoporphycene is slower than in corrphycene ($\Delta G^{\ddagger}$ = 13.5 kcal mol^{-1}), and this difference was explained in terms of weaker hydrogen bonding in the more distorted trapezoidal core of isoporphycene. The isomerism of

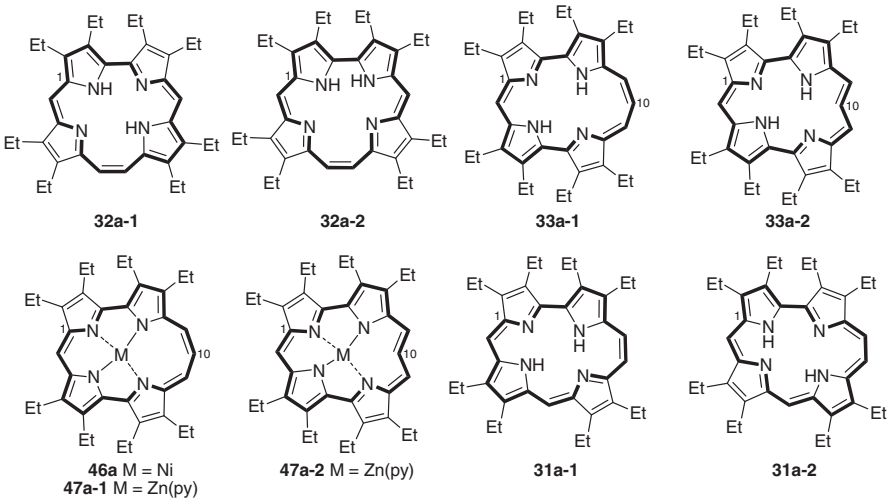


Fig. 20 Other porphyrin isomers

isoporphycene is affected by metal complexation, and the isoporphycene Ni(II) complex **46a** was observed to form the *Z* isomer exclusively. In contrast, the (pyridine)zinc(II) complex was isolated as a 40:60 mixture of *Z* and *E* isomers **47a-1** and **47a-2**. Both isomers were also observed in the case of Pd(II) isoporphycene, for which the isomerization process was triggered by light [145].

Unlike all the porphyrin isomers discussed above (including porphyrin itself), hemiporphycene **31** possesses two nonequivalent *trans*-protonated tautomers, even in the case of symmetrical peripheral substitution. The two tautomers **31a-1** (22*H*,24*H*) and **31a-2** (21*H*,23*H*) were identified in the ^{1}H NMR spectrum recorded at low temperatures, with a concentration ratio of 7:1. This was in agreement with theoretical calculations, which predicted a marginally higher energy for tautomer **31a-2**.

2.5 Expanded Porphyrins

According to a recently proposed definition, expanded porphyrins possess more than 16 atoms in the inner or, more precisely, smallest circuit of the macrocycle (porphyrin **1** contains exactly 16 atoms in the smallest macrocyclic circuit) [11]. In addition to porphyrinoid macrocycles traditionally recognized as "expanded," i.e., possessing more than four cyclic subunits or more than four *meso* bridges, this new definition encompasses some other systems, such as *p*-benziporphyrin **150**. Regardless of the exact definition, expanded porphyrins constitute an unusually rich and diverse family of structures, and have been the subject of several excellent reviews [2, 5, 11, 146]. The relationship between aromaticity and tautomerism in

expanded porphyrins is often complicated by the occurrence of conformational equilibria and multiple redox states of the macrocycle. In general, antiaromaticity is easier to attain in expanded porphyrins than in smaller rings [11], an effect that can be attributed to the decreasing difference between resonance stabilization energies of $4n$ and $4n + 2$ systems for larger values of n [29]. The conformational freedom of expanded macrocycles makes their aromatic properties more difficult to predict, as exemplified by the recently discovered Möbius aromatic porphyrinoids [147–148] (see also [149]). In the discussion below, sapphyrins and cyclopyrroles have been chosen to provide representative examples of the most important aspects of aromaticity in expanded porphyrinoids.

2.5.1 Sapphyrins

Sapphyrins or [22]pentaphyrins(1.1.1.1.0) are formally derived from porphyrins by insertion of an additional pyrrole ring into the macrocycle (**48**, Fig. 21) [150]. The resulting structure possesses three mobile protons in the core, and contains a [22]annulenoid pathway corresponding to macrocyclic aromaticity. First β-substituted sapphyrins were synthesized by R.B. Woodward and coworkers in the 1960s [151–153], whereas their *meso*-aryl congeners were made available much later [154, 155]. The larger dimensions of the sapphyrin ring result in a more pronounced ring current than that in regular porphyrins. For instance, the *meso* protons in the dichloride salt of **48b** resonate at ca 11.7 ppm whereas the inner NHs give signals at –4 to –5 ppm [156].

There are six distinct tautomers of unsubstituted free base sapphyrin, of which **48a-1** (shown in Fig. 21) was predicted to have the lowest energy by DFT calculations [157]. However, the next most stable tautomer of **48a** (namely 25*H*,27*H*,29*H*) was only 1.4 kcal mol^{-1} higher in energy (B3LYP/6-31G**//3-21G), indicating that the energy ordering may be easily affected by peripheral substitution or solvent effects. Variable-temperature ^{1}H NMR data obtained for **48b** in dichloromethane-d_2 revealed the presence of several rapidly exchanging tautomers, which at higher temperatures are additionally involved in reversible coordination of water molecules in the macrocyclic cavity [158]. These complicated results explain why it is customary to characterize sapphyrins and other expanded porphyrins as acid salts, whose ^{1}H NMR spectra are much easier to interpret.

A particularly interesting feature of the sapphyrin nucleus is its conformational flexibility, which is affected by peripheral substitution and protonation equilibria. As discussed above, the β-substituted derivative adopts a planar conformation **48b-1** both as the free base and dication, an observation that is in agreement with the theoretical predictions for the unsubstituted sapphyrin **48a** [157]. In sharp contrast, *meso*-tetraphenylsapphyrin takes on a "ring-inverted" structure **48c-2**, wherein pyrrole ring C is flipped to the inside of the macrocycle [154]. As a result, the β-protons of pyrrole C (12,13-H) and the corresponding NH (27-H) exchange their positions relative to the anisotropy cone of the macrocycle. Specifically, in the ring-inverted structure, proton 27-H is located in the deshielding zone and resonates at

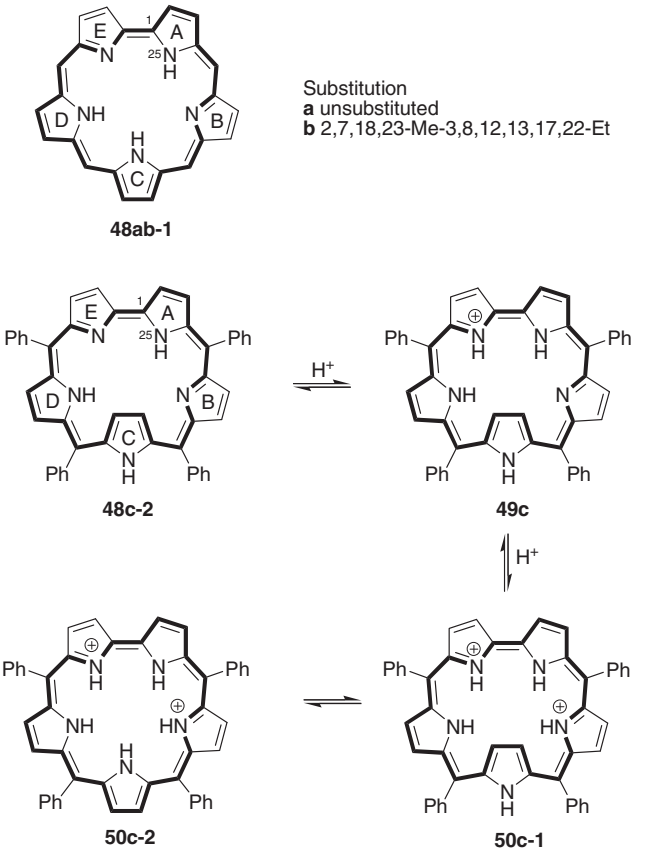


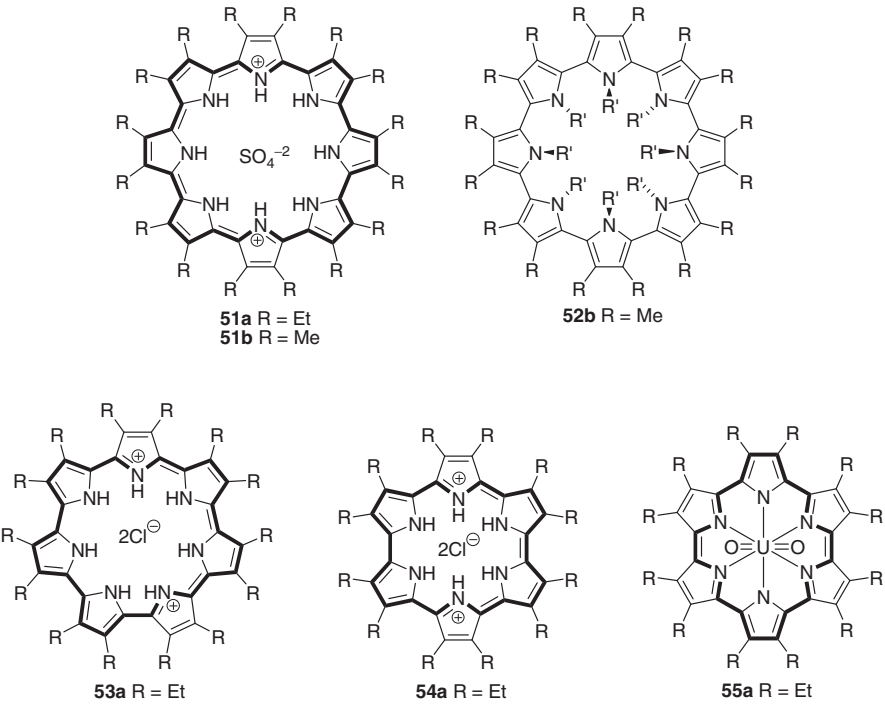
Fig. 21 Sapphyrins

12.24 ppm, whereas the β-protons are shielded and their signal is shifted to -1.50 ppm. It should be noted that the inverted pyrrole ring in **48c-2** is not coplanar with the macrocycle, because of steric repulsions in the core. According to DFT calculations, ring inversion in **48c-2** is caused by steric interactions with the flanking *meso* substituents (10,15-Ph), which make the ring-inverted structure energetically favorable [157]. In fact, ring inversion is not unique to **48c-2** but has also been observed in a number of *meso*-aryl heterosapphyrins [159–161] and other expanded porphyrins, such as those discussed in Sect. 3.2.6. Interestingly, ditelluraporphyrin (**81b**, Sect. 3.1) provides an example of ring inversion in a nonexpanded system. A related conformational change was observed in a C(21)–C(21′) linked N-confused porphyrin dimer [162] and postulated for the monomeric N-confused porphyrin (transient species **108-2**, Sect. 3.2.5). Apart from the steric influence, *meso*-aryl substitution has an effect on the electronic structure of sapphyrins, leading for instance to the reversal of the relative magnitude of HOMO and LUMO splittings, which affects the magnetic circular dichroism spectra of these macrocycles [163].

The reversal of shielding effects was not observed in the ^{1}H NMR spectrum of the dichloride salt of **48c** recorded in chloroform-*d*, indicating that the macrocycle unfolded into a planar structure upon protonation [154]. Systematic studies revealed that protonation of **48c** triggers complicated equilibria, which involve, in addition to the free base, the ring-inverted monocation **49c** and two distinct conformations of the dication (**50c-1** and **50c-2**) [164]. The equilibrium between the latter two forms was found to depend on the amount of excess acid added and the solvent.

2.5.2 Cyclo[*n*]pyrroles

Expanded porphyrins possessing no *meso* bridges are known as cyclo[*n*]pyrroles. To date, three of these highly symmetrical structures have been synthesized, containing respectively six, seven, and eight directly linked pyrrole rings (Fig. 22). In the most important member of this class, cyclo[8]pyrrole, the macrocyclic cavity provides a perfect match for the sulfate ion, and the compound is preferably



51a R = Et
51b R = Me

52b R = Me

53a R = Et

54a R = Et

55a R = Et

Fig. 22 Cyclo[*n*]pyrroles

isolated as the sulfate salt **51** [165]. The macrocycle in **51** possesses a 30-π electron conjugation pathway, and can be alternatively termed [30]octaphyrin(0.0.0.0.0.0.0.0). Accordingly, the macrocycle, which is reasonably planar, shows distinct aromaticity. In the room-temperature ^{1}H NMR spectrum of **51a**, the NH signal is observed at 0.64 ppm and shifts farther upfield as the temperature is lowered. The aromatic delocalization has a particularly striking effect on the electronic spectrum of **51a**, which contains an absorption at 1,112 nm that is broad and very intense (log ε = 5.12) [165]. The smaller congeners of **51a**, cyclo[7]pyrrole (dichloride salt **53a**) and cyclo[6]pyrrole (dichloride salt **54a**), are also aromatic, possessing respectively 28- and 22-electron pathways [166]. On moving to smaller ring sizes, the red shift of the Q band decreases as expected. However, ring currents cannot be quantitatively compared on the basis of ^{1}H NMR data, as they are likely dependent not only on the ring size but also on the degree of ruffling and the identity of the counteranion.

Redox behavior of cyclopyrroles is worth a special mention. Cyclo[8]pyrrole salt **51a** undergoes a reversible two-electron reduction at –0.08 V (vs. SCE), whereas only one-electron processes were observed for the smaller homologs (-0.18 V for **53a**; –0.35 V and –0.48 V for **54a**) [165]. Additionally, the HOMO–LUMO gap in cyclo[*n*]pyrroles decreases with increasing ring size (1.30 V, 0.85 V, 0.60 V for n = 6, 7, 8). These data confirm that these systems are much more strongly conjugated than regular porphyrins, which typically exhibit HOMO–LUMO gaps of 2.25 ± 0.15 V [167].

Cyclo[8]pyrrole can also be reduced chemically to yield octa-N-substituted derivatives of [32]octaphyrin(0.0.0.0.0.0.0.0) of the general structure **52b** (R′ = Me, Et, Bn) [168]. These macrocycles, characterized by a formally antiaromatic π-electron count, are strongly nonplanar, with the R′ substituents alternating their positions in an up-and-down fashion. As a result, these molecules show little if any macrocyclic conjugation and exhibit no paratropicity. This lack of conjugation has a remarkable influence on the electronic spectra of **52b**, which contain no significant absorptions in the region 325–1,100 nm. The compounds are essentially colorless but can be converted into strongly absorbing dications by two-electron electrochemical oxidation. These dications have electronic absorption profiles similar to those of the cyclo[8]pyrrole salts **51** bearing no internal substituents.

Parallel experiments carried out with cyclo[6]pyrroles showed that only the hexa-*N*-methyl derivative could be efficiently obtained, most likely because of steric limitations [169]. Interestingly, however, cyclo[6]pyrrole **54a** was found to coordinate the uranyl cation $[UO_2]^{2+}$ with a concomitant two-electron oxidation of the macrocycle to a [20]annulenoid structure **55a** [170]. As expected, this system is strongly paratropic, as evidenced by the shielding of peripheral ethyl substituents in the ^{1}H NMR spectra (–1.42 ppm for CH_2 and –1.12 ppm for CH_3). Additionally, electronic absorptions of **55a** are much less intense that those of the free base **54a**.

2.6 Contracted Porphyrins

2.6.1 Corroles and Related Systems

In analogy to the definition used above for expanded macrocycles, contracted porphyrins may be defined as possessing less than 16 atoms in the smallest macrocyclic circuit. This family of macrocycles is typified by corrole **56**, the most widely studied contracted porphyrin, and its heteroanalogs [9,146]. Corroles, available with both *meso*- (e.g., **56a**, Fig. 23) and β-substitution (e.g., **56bc**) [171–173], possess four pyrrole rings and only three *meso* bridges, creating an aromatic 18-π electron structure. As a consequence of ring contraction, corrole contains three NH protons inside a macrocyclic core that is distinctly smaller than that of porphyrin. Of the two possible tautomers of corrole, **56-1** was actually observed in the X-ray structure of **56d**, which did not suffer from positional disorder of the inner hydrogens [174]. In this structure, the macrocycle shows a slight up-and-down tilting of the pyrrole rings, necessary to reduce steric repulsions in the core. Tautomer **56-2**, bearing two NH protons on the bipyrrole unit, was previously proposed on the basis of molecular calculations and an early X-ray structure of **56b** [175, 176]. The energy difference between unsubstituted **56-2** and **56-1** was predicted to be only 2.45 kcal mol^{-1}, suggesting that the tautomerization in corroles may be faster than in the case of porphyrins [177].

The steric congestion resulting from ring contraction is probably responsible for the relative acidity of corroles, which, unlike porphyrins, form stable monoanions

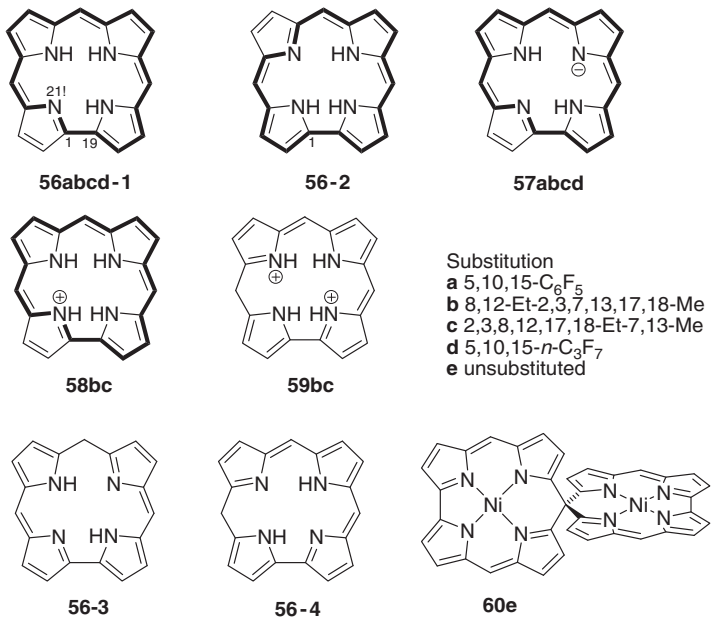


Fig. 23 Corroles and related systems

of type **57** when treated with alkali [171]. In fact, the *meso*-substituted system **56a** forms a dianion in ethanolic solutions, and is readily deprotonated by weak bases when dissolved in less polar organic solvents [173]. Corroles are protonated in two steps, forming an aromatic monocation **58** and a nonaromatic dication **59**. In the latter species, macrocyclic conjugation is broken by protonation of one of the *meso* positions, leading to an observable lack of diatropicity in the ^{1}H NMR spectrum and to the disappearance of the Soret band from the electronic spectrum of **59** [178]. More recently, protonation equilibria in a variety of substituted corroles, including systems substituted with basic groups, were investigated in nonaqueous media using electro- and spectroelectrochemical methods [179, 180].

While *meso*-protonation of corrole was observed in strongly acidic media (structure **59**), no *meso*-protonated tautomers of free base corroles (**56-3** and **56-4**) have been observed. However, non-aromatic corrole derivatives related to **56-3** and **56-4** are known, containing two substituents on the saturated *meso* bridge [181–184]. Such a double substitution prevents these structures from tautomerizing to fully conjugated corrole structures. In a particularly interesting dimeric system of this kind, called spirodiisocorrole (**60e**) [181, 182], the two subunits have been shown to display effects of so-called spiroconjugation, resulting from the overlap of two perpendicular π systems [185, 186].

A (2.0.1.0) isomer of corrole (variously known as isocorrole or corrolene, **61**) has been synthesized, which retains the [18]annulenoid aromaticity of **56** in spite of additional strain (unsubstituted **61** is predicted to be ca. 3.5 kcal mol^{-1} higher in energy than **56**) [187, 188]. Interestingly, ^{1}H NMR spectra and X-ray structures obtained for the two substitution variants **61a** and **61b** revealed that each of them exists predominantly as a differently protonated tautomer (**61a-1** and **61b-2**, respectively, Fig. 24). Specifically, inner NH protons resonated at 6.18 and -1.20 ppm in **61a-1** (21-H and 22,23-H, respectively) [188] and at 3.5 and -2.5 ppm NH in **61b-2** (22-H and 21,24-H) [187], indicating that in each case the "lonely" proton is involved in hydrogen bonding, which leads to an upfield shift of the corresponding signal.

Attempts to synthesize corrole macrocycles occasionally lead to structurally exotic products, such as **62** or **63** [189, 190]. Formation of such systems, containing "*ortho*-disubstituted" cyclic subunits, is favored, because they are less strained than the isomeric corrole-like macrocycles. Both the dioxacorrole isomer **62** and "corrorin" **63** adopt highly nonplanar conformations and are nonaromatic, even though the latter species possesses a [14]annulenoid circuit. Interestingly, **63** undergoes a ring opening reaction, which results in the formation of the diatropic "oxoindolophyrin" **64**, in which an [18]annulenoid pathway is available through the dipolar contribution **64′**.

2.6.2 Subporphyrins and Related Systems

In corroles and other systems described above, the macrocyclic ring is contracted by leaving out one of the four porphyrinic *meso* bridges. A more radical modification, namely an omission of one the cyclic subunits, results in even smaller macrocyclic rings, collectively termed triphyrins. Boron subphthalocyanines (**65**, Fig. 25), known for 35 years [191], are an archetype of triphyrin structure. However, their

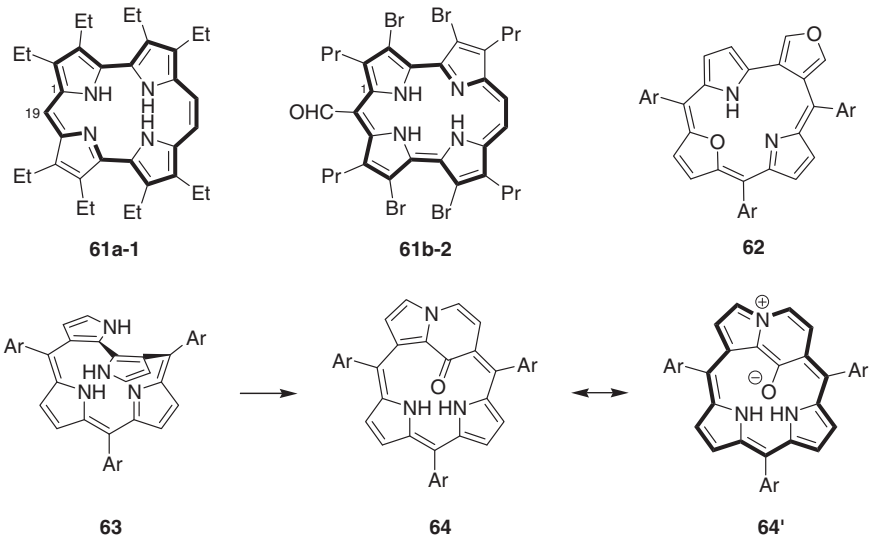


Fig. 24 Corrole isomers and related systems

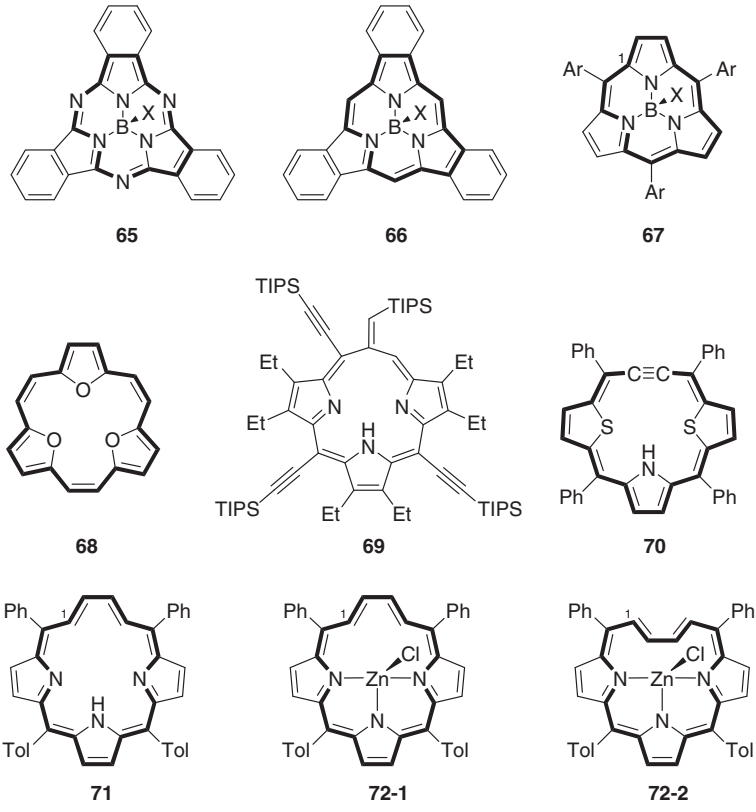


Fig. 25 Subporphyrins and related structures

all-carbon-linked analogs, such as **66** and **67**, have been synthesized only very recently. Both tribenzosubporphyrins (**66**) [192] and 5,10,15-triarylsubporphyrins (**67**) [193, 194] were obtained on a boron template, which remains in the macrocyclic product as an integral part of the structure (for an alternative synthesis of subporphyrins by extrusion from an expanded porphyrin see [195]). All these molecules, classifiable as triphyrins(1.1.1), are bowl-shaped, and their ^{1}H NMR and electronic spectra exhibit features expected of an [14]annulenoid aromatic system. A related molecule, subpyriporphyrin, which was obtained without the use of a boron template, is discussed in Sect. 4.2.2.

By introducing additional *meso* carbons into the triphyrin structure, it is possible to construct other contracted systems, which are possibly less strained than the original (1.1.1) structure. Triply bridged [18]annulenes, such as the trioxide **68** [196], may be considered heteroanalogs of the unknown NH-bridged structure, triphyrin(2.2.2). Compound **68** is aromatic but other heteroanalogs, especially those containing thiophene rings, may be polyenic, as discussed in detail in [146].

Another possibility for expanding the triphyrin structure is by stepwise homologation of one of the *meso* bridges. While no attempt to create a homologous series of this kind has yet been made, a number of disparate molecules can be included in this category. A triphyrin(3.1.1) ring system is found in compound **69**, which however contains an exocyclic double bond and is consequently nonaromatic [197]. Dithiaethyneporphyrin **70**, which may be considered a derivative of triphyrin(4.1.1), is aromatic and possesses an [18]annulenoid conjugation [198]. Finally, vacataporphyrin **71**, an aromatic porphyrin derivative (so-called because of the "vacated" heteroatom site) is a triphyrin with the (6.1.1) bridging pattern [199]. However, vacataporphyrin no longer meets the new definition of a contracted porphyrinoid, as the smallest macrocyclic circuit in **71** contains 17 atoms. Metal complexes of vacataporphyrin exhibit a peculiar type of isomerism exemplified by the two forms of the chlorozinc(II) complex **72-1** and **72-2** [200]. In the latter form, the 1,3-butadiene-1,4-diyl linker is inverted in the macrocyclic frame, and the resulting out-of-plane deformation of the ring causes a marked reduction in the observed diatropic ring current.

3 Systems Containing Five-Membered Rings

3.1 Heteroporphyrins

In heteroporphyrins, at least one of the pyrrolic nitrogens is replaced with a different atom, usually a chalcogen. Examples of pertinent structures are given in Fig. 26. The chemistry of heteroporphyrins was reviewed in detail in [6, 201, 202]. Here we will highlight the most characteristic features of aromaticity and tautomerism in heteroporphyrins, with an emphasis on the more recent synthetic advances in the field.

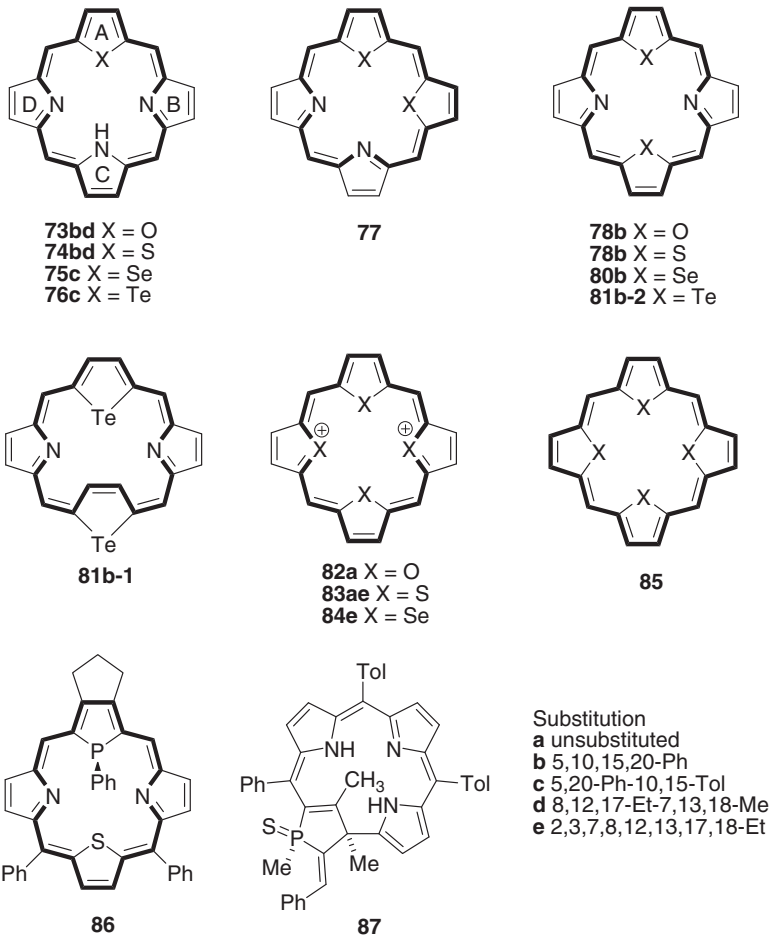


Fig. 26 Heteroporphyrins

Introduction of a single chalcogen atom (X = O [203, 204], S [204, 205], Se [206], or Te [207]) in place of one of the NH groups produces the corresponding 21-heteroporphyrins (**73**–**76**). These systems are aromatic with a preferred 18-π electron conjugation pathway that circumvents the heteroatom site, as can be inferred from crystallographically determined bond length patterns (cf. [208]). Monoheteroporphyrins possess one mobile proton in the macrocyclic core, which resides on the nitrogen opposite the heteroatom. In β-unsubstituted systems (e.g., **74b**), β-protons attached to rings A and C (especially the former) exhibit more downfield shifts than those attached to rings B and D, additionally confirming the preference for the annulenoid circuit indicated in Fig. 26.

In 21,23-diheteroporphyrins (**78**–**81**), the preferred conjugation pathway is identical with that observed in the monoheteroporphyrins. The much less explored

21,22-diheteroporhyrins of the general structure **77** are reviewed in [6]. Available spectroscopic data indicate that 21,23-diheteroporphyrins containing O [203], S [209], and Se [210] adopt planar or moderately ruffled conformations with all heteroatoms directed towards the center of the macrocycle. Surprisingly, the tellurium analog was found to prefer conformation **81b-1**, in which one of the tellurophene rings is inverted, as shown in Fig. 26 [211]. However, the inverted ring is not coplanar with the rest of the macrocycle, but is tilted at an angle of 57°. The two tellurophene rings are subject to rapid inversion in solution, most likely with the intermediacy of the uninverted, though probably still nonplanar, structure **81b-2**. In spite of its nonplanarity, 21,23-ditelluraporphyrin **81b-1** is moderately aromatic, with the β-tellurophene protons resonating at 8.53 and 6.08 ppm. The latter shift corresponds to the inverted ring, which is not located in the macrocyclic plane and thus experiences only a weak shielding effect. The different behavior of **81b** relative to other 21,23-diheteroporphyrins is a consequence of the steric requirements of the Te atom but also of the different geometry and electronic structure of the tellurophene ring.

Replacement of all four nitrogens of the porphyrin with chalcogen atoms requires that the resulting structure be dicationic if the overall oxidation level of the molecule is to be retained. Such dications (**83**–**84**) were indeed obtained containing X = O [212, 213], S [214, 215], and Se [216], and were found to exhibit porphyrin-like macrocyclic aromaticity. By two-electron reduction, each of these systems can be reversibly converted into the corresponding neutral form of the general structure **85**. These antiaromatic molecules, which are directly related to isophlorins (**18**, Sect. 2.3.3), contain [20]annulenoid circuits with distinct double bond localization [113, 215]. Interestingly, the tetraselenaporphyrin dication **84e** can be reduced even farther, yielding an aromatic 22-π electron dianion [216].

Extending the idea of heteroatom replacement beyond the chalcogen group is synthetically demanding, and consequently very few examples are known. 21-Phospha-23-thiaporphyrin **86** possesses full macrocyclic conjugation and is actually aromatic [217]. Very recently, its tripyrrolic analog was also reported, along with an unusual 20-π electron antiaromatic derivative [218]. Interestingly, independent attempts to synthesize phosphaporphyrins resulted in the unexpected formation of a P-confused phosphacorrole derivative **87** with interrupted macrocyclic conjugation [219].

3.2 Ring-Confused Systems

3.2.1 N-Confused Porphyrin

The structure of N-confused porphyrin **88** (Fig. 27) was first proposed in 1943 by S. Aronoff and M. Calvin (the future Nobel laureate) during a reexamination of Rothemund's synthesis of tetraphenylporphyrin [47]. However, no convincing proof for such a structure was provided and only two of the six pigments isolated

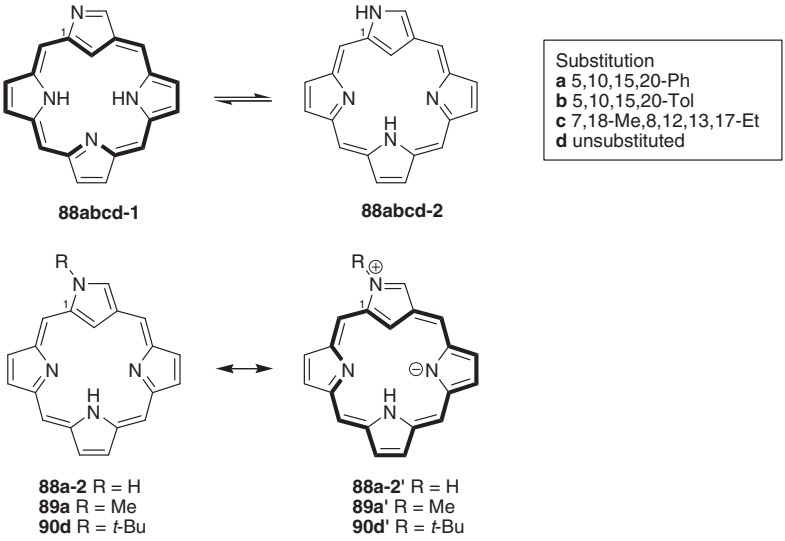


Fig. 27 N-confused porphyrins

by the authors were ultimately identified (as tetraphenylporphyrin and tetraphenylchlorin, respectively). Fifty years later, *meso*-substituted N-confused porphyrin (**88a-b**) was isolated as a byproduct in the Lindsey synthesis of *meso*-aryl porphyrins [220, 221]. β-Substituted [222, 223] and unsubstituted [224] N-confused porphyrins were later obtained in directed syntheses. Subsequent research revealed unusual physical and chemical properties of N-confused systems, in particular their unorthodox coordination chemistry.

In its principal tautomeric form **88a-1**, N-confused tetraphenylporphyrin is doubly N-protonated inside the macrocyclic core, retaining an imine-like peripheral nitrogen. Tautomer **88a-1**, observed in the solid state and in chloroform solutions [220, 221], exhibits distinct macrocyclic aromaticity, comparable with that of regular porphyrins. The magnitude of the ring current, as judged by ^{1}H chemical shifts, is similar in regular and N-confused porphyrins, and so are the UV–vis molar absorptivities. This aromaticity is in accord with the [18]annulenoid conjugation pathway found in **88a-1**, which is analogous to that discussed earlier for porphyrins.

When **88a** is dissolved in *N*,*N*-dimethylformamide (DMF), it is completely transformed into tautomer **88a-2**, protonated on the peripheral nitrogen [223–225]. This tautomer is stabilized by a H-bonded interaction with DMF, and was also characterized crystallographically in a DMF-solvated crystal [225]. In vacua, the energy difference between tautomers **88d-1** and **88d-2** calculated by DFT methods is around 5 kcal mol^{-1} [226, 227]. Conversion of **88a-1** into **88a-2** is associated with a remarkable change of the UV–vis spectrum indicating a different electron delocalization pattern. In the ^{1}H NMR spectrum of **88a-2**, the signals corresponding to

the inner CH and NH protons were found at 0.76 and 2.27 ppm, respectively, i.e., they were relocated downfield relative to the corresponding shifts in **88a-1** (–4.99 and -2.41 ppm) [225]. The residual diatropicity of **88a-2** can be explained in terms of the dipolar resonance contribution **88a-2′**, possessing an [18]annulenoid pathway. A similar argument may be used to explain the weaker aromatic character of the 2-substituted derivatives of **88** such as **89a**, which can be thought of as frozen models of the **88-2** tautomer. Judging by the ^{1}H chemical shifts, the dipolar contribution is apparently even smaller in **89a** than in **88a-2** [228].

The influence of tautomerism on aromaticity observed in N-confused porphyrin is echoed in the properties of its metal complexes. Depending on the oxidation state of the metal ion, the macrocycle adjusts its protonation level to yield a neutral complex. Divalent ions, such as Ni(II) [220], preferably form complexes of the general formula **91** (Fig. 28), whereas trivalent ions, such as Ag(III) give structures

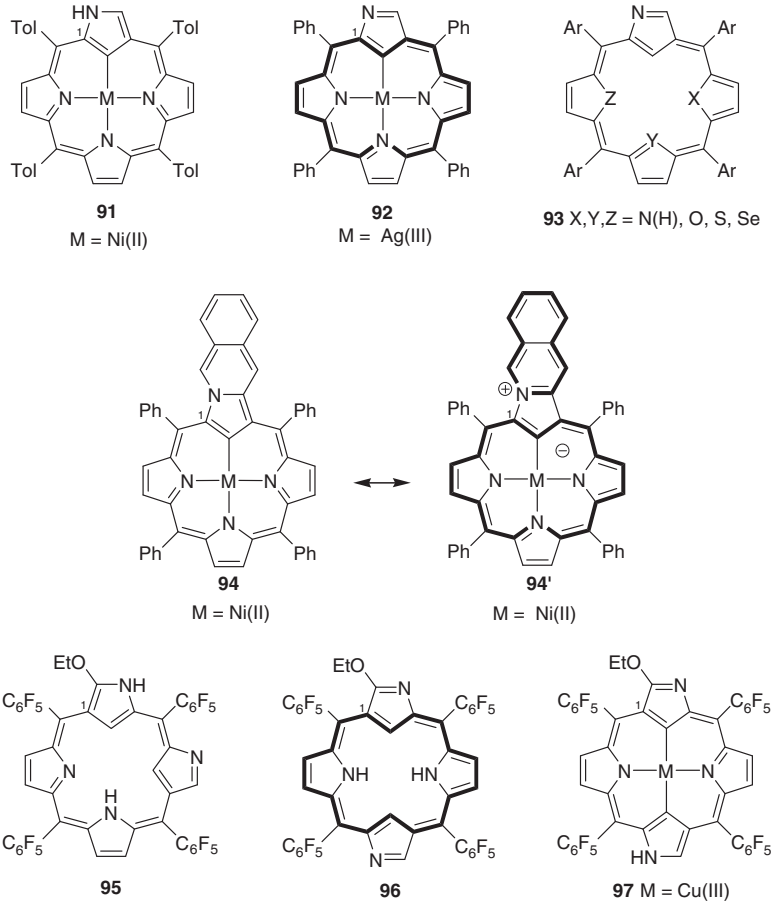


Fig. 28 Singly and doubly N-confused porphyrins

of type **92**, which lack the peripheral NH [229]. The relationship between these two structures is similar to that between tautomers **88-1** and **88-2**, and has a comparable effect on the macrocyclic aromaticity. Interestingly, the structurally related nickel(II) complex **94**, possessing an isoquinoline unit fused to the N-confused ring, displays significant macrocyclic diatropicity, indicating a sizable contribution of the charge-separated canonical structure **94′** [230] (see also [231]). It should be noted that in the case of **94**, charge separation additionally enables cyclic conjugation in the peripherally fused isoquinoline unit, an effect that likely contributes to the relative stability of **94′**. Prototropic tautomerism and protonation were also explored in a number of N-confused heteroporphyrins of the general structure **93**, containing one or two chalcogen atoms in the core [160, 232–234]. These compounds are generally involved in rather complex tautomeric exchange, often resulting in complicated dynamic ^{1}H NMR spectra.

3.2.2 Multiply N-Confused Porphyrins

Extension of the confusion concept to multiply N-confused systems, while conceptually simple, is rather difficult to achieve through synthesis. To date, no multiply confused porphyrins have been obtained in stochastic (Rothemund-type) syntheses. A doubly N-confused porphyrin, namely 2-ethoxy-3,7-diaza-21,22-dicarbaporphyrin **95** (Fig. 28) was obtained from a predesigned "N-confused" precursor [235]. The peripheral ethoxy substituent was spontaneously incorporated in the product, and attempts to obtain the 2-unsubstituted macrocycle were unsuccessful. The only observed tautomer of **95** bears one of the labile hydrogens on one of the peripheral nitrogens, and this protonation pattern is retained in complexes of **95** with Cu(III) and Ag(III). Therefore, **95** has a conjugation pattern similar to that in the peripherally protonated singly N-confused porphyrin (**88-1**) and likewise exhibits reduced macrocyclic aromaticity. To achieve an aromatic [18]annulenoid structure, **95** would need to be protonated on both of the inner nitrogens, leading to a sterically congested structure [236]. Protonation of **95** occurs in two separate steps, as in the case of the singly N-confused isomer. Interestingly, the peripheral NH in **95** is easily removed by weak bases such as triethylamine. An intense Soret band appears in the electronic spectrum of **95** upon deprotonation, suggesting an increase of macrocyclic aromaticity [237].

In a subsequent study it was reported that compound **96**, which is the *trans* isomer of **95**, exhibits a preference for [18]annulenoid conjugation [238]. Both X-ray and NMR data confirmed that the two mobile protons reside in the macrocyclic core, leading to a system with distinct diatropicity. Interestingly, upon coordination of Cu(III), the macrocycle switches to the formally cross-conjugated structure **97** with somewhat reduced aromaticity. In analogy to the behavior of singly N-confused porphyrin, the aromaticity type selected upon complexation depends on the matching between the formal charges of metal ion and macrocyclic core.

Stability and aromaticity of multiply N-confused porphyrins were systematically investigated using DFT calculations [236, 239]. Ignoring tautomerism, there are

respectively five, four and four distinct isomers of doubly, triply, and quadruply N-confused porphyrins. The DFT-optimized structures displayed a great variability of relative energies (over 80 kcal mol^{-1}) and center NICS values (from 0 to −15 ppm), both of which showed systematic dependencies on the confusion number and protonation pattern. It was found that each additional N-confusion destabilized the macrocycle by approximately 18 kcal mol^{-1}. Center NICS values provided a good quantitative descriptor of aromaticity. In structures possessing formal [18]annulenoid pathways, the NICS shifts were systematically lower (by 4–7 ppm) than in their "cross-conjugated" tautomers. It was observed that macrocyclic aromaticity had no particular correlation with relative energy, the latter being apparently more dependent on steric factors (many of the structures obtained were heavily distorted).

3.2.3 Oxidized N-Confused Porphyrins

In "carbachlorin" **98** (Fig. 29), the peripheral part of the N-confused ring is oxidized to a lactam function [240]. Such a modification does not interfere with the macrocyclic aromaticity, and no tautomeric equilibria involving the oxidized ring have been reported. 21-Hydroxy-N-confused porphyrin **99** possesses an additional mobile proton that could be involved in prototropic tautomerization [241]. This compound is analogous to the derivatives of azuliporphyrin and benziporphyrin oxidized at the internal carbon (see Sects. 3.3.2 and 4.1.2) but its tautomeric behavior in solution was not disclosed. However, DFT calculations were performed suggesting that a paratropic keto tautomer of **99** might have stability comparable with that of the hydroxy species. Structural data obtained for metal complexes of **99** revealed that the inner C–O bond has a length of 1.30–1.38 Å [242, 243]. The shortest distance, observed in a bromoiron(III) complex is shorter than the corresponding bond lengths in typical aryloxide ligands, indicating a small keto admixture to the resonance hybrid [243].

3.2.4 X-Confused Systems

The N-confusion concept can be generalized to heterocyclic rings other than pyrrole. The resulting systems, known as X-confused porphyrinoids (Fig. 30), structurally

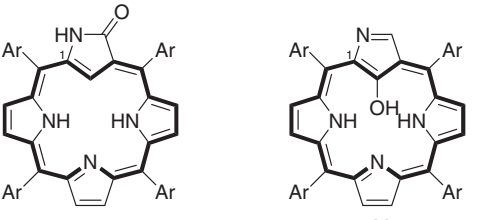


Fig. 29 Oxygen-substituted derivatives of N-confused porphyrin

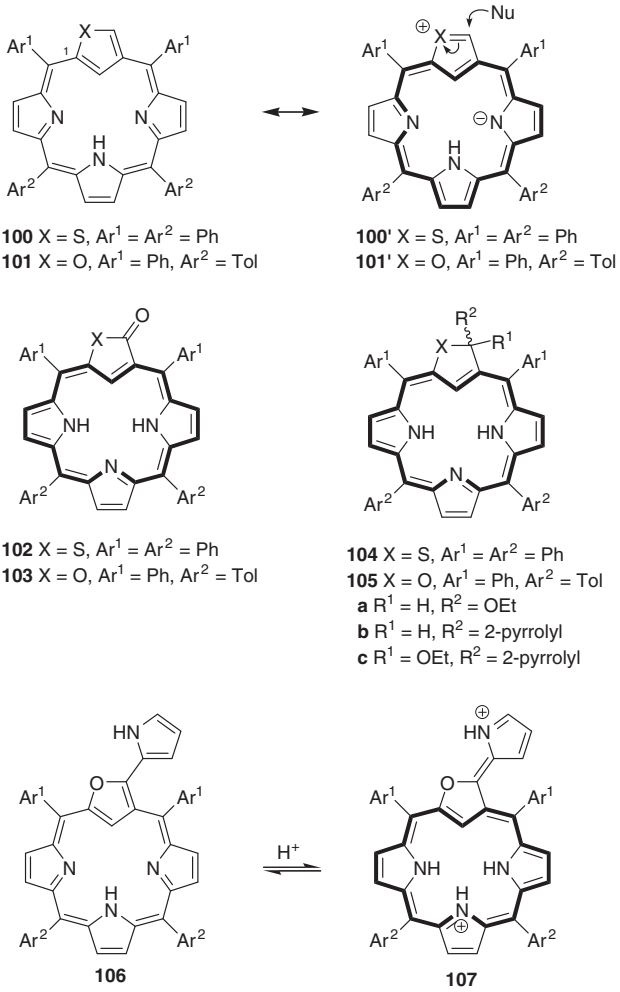


Fig. 30 X-confused porphyrins

resemble N-confused porphyrins, but their tautomerism is limited because of the absence of the external protonation site. Still, they are capable of forming organometallic complexes with a variety of transition metal ions, including Ni, Pd, Cu, and Ag [16, 244]. In contrast to N-confused porphyrinoids, which are frequently available from stochastic syntheses, the preparation of X-confused heteroporphyrins requires multistep procedures and the resulting products are often quite reactive. The origins of this reactivity can be traced to the unusual electronic structure of these systems. 2-Thia-21-carbaporphyrin **100** is a moderately stable species that undergoes reactions at the free a-thiophene position [245]. Its furan analog **101** is

much more reactive and its isolation (in the form of an acid salt) required considerable effort [16, 246]. Contributions of the charge-separated canonical structures **100′** and **101′**, which imply the onium character of the peripheral heteroatom in **100** and **101**, increase the reactivity of position 3 towards nucleophiles, leading to the formation of a variety of 3-substituted species (**102**–**105**) [16]. This reactivity is reminiscent of the spontaneous 2-substitution in doubly N-confused porphyrin **95**.

The X-confused systems **100** and **101** exhibit borderline macrocyclic aromaticity, which results from the onium-type contributions **100′** and **101′**, characterized by the presence of 18-electron aromatic circuits. For instance, the NH protons in **100** resonate at ca. 5.8 ppm, while those in the corresponding dication are observed at 5.3–4.4 ppm. These chemical shifts are intermediate between values expected of a nonaromatic porphyrinoid ($\delta > 10$ ppm) and those typical of aromatic systems ($\delta < 0$ ppm). The macrocyclic aromaticity is fully restored in the 3-substituted derivatives containing an sp^3 carbon (**104**–**105**) or a carbonyl group (**102**–**103**), which is an additional reason for the enhanced reactivity of **100** and **101**. In comparison, the pyrrolyl-substituted derivative **106** shows only moderate diatropicity, which is noticeably enhanced upon protonation [247]. This effect is explained by cross-conjugation of the pyrrolyl substituent in the dication **107**, which enables an 18-electron aromatic circuit in the macrocycle.

3.2.5 N-Fused Porphyrin

A number of 3-bromo-substituted derivatives of N-confused porphyrin (**108a–d**, Fig. 31) were shown to undergo a very unusual reaction known as N-fusion [248, 249]. The reaction most likely begins with an "inversion" of the N-confused ring and formation of structure **108-2** (similar to the conformational change observed in sapphyrin **48c**). DFT modeling indicates that the inversion of the N-confused ring in **88d** requires ca. 18.5 kcal mol^{-1}, much less than the inversion of a protonated pyrrole ring in porphine [250]. In the postulated inverted intermediate **108-2**, the bromoimine fragment of the N-confused pyrrole reacts with an adjacent nitrogen atom in the macrocycle to form a new N–C bond (see [162] for a N-confused porphyrin dimer locked in a doubly inverted conformation). The resulting system, termed N-fused porphyrin (**109**), reveals the truly remarkable flexibility of the porphyrin ring. In spite of such a severe distortion from the planar structure, the [18]annulenoid circuit survives in the N-fused porphyrin, circumventing the newly formed amidine grouping (N2 = C3–N22). While the shifts of the peripheral protons in N-fused porphyrins indeed correspond to strong diatropicity (7.5–9.0 ppm), the inner NH signal is unexpectedly shifted downfield to ca. 8.4 ppm. This shift was interpreted as an effect of very strong intramolecular hydrogen bonding, which outweighs the ring current effect. In a 17,18-dibromo derivative of N-fused porphyrin, the tautomeric preference of the macrocycle was altered and **109f-2** was observed as the principal tautomer [249]. This effect of bromine substitution, which favors isolation of the adjacent C_β–C_β bond from the macrocyclic circuit, is similar to that observed in 2-bromo-*meso*-tetraphenylporphyrin (**3-Br**, Sect. 2.3.1).

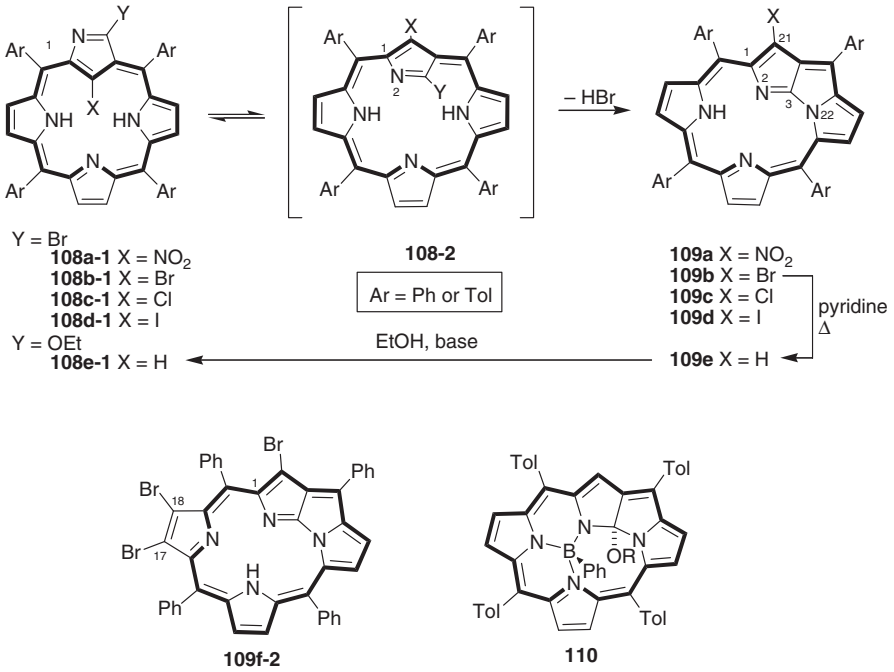


Fig. 31 N-fused porphyrins

In spite of its unusual structural outcome, the N-fusion reaction is a very general process. It was observed in a number of other N-confused macrocycles. For instance, an N-fused intermediate forms in the synthesis of *trans* doubly N-confused porphyrin **96** [238]. N-fusion was also induced by the reaction with $PhBCl_2$, in which case the reaction was promoted by the small radius of the coordinating boron(III) center [251]. The resulting boron complexes were also aromatic, even though in some cases further chemical modification of the macrocycle took place (as in **110**). The fusion process, which appears to be a nucleophilic addition–elimination, is reversible, and N-fused macrocycles can often be "reopened" when treated with nucleophiles such as alkoxides [248, 249].

3.2.6 Other N-Confused Macrocycles

A number of N-confused systems are known with macrocyclic conjugation interrupted by sp^3 *meso* bridges. These systems, which include analogs of calixpyrroles [252] and calixphyrins [253], fall outside the scope of the present review. A number of fully conjugated N-confused expanded porphyrins have been obtained by use of predesigned N-confused substrates. The most representative examples of such structures are collected in Fig. 32.

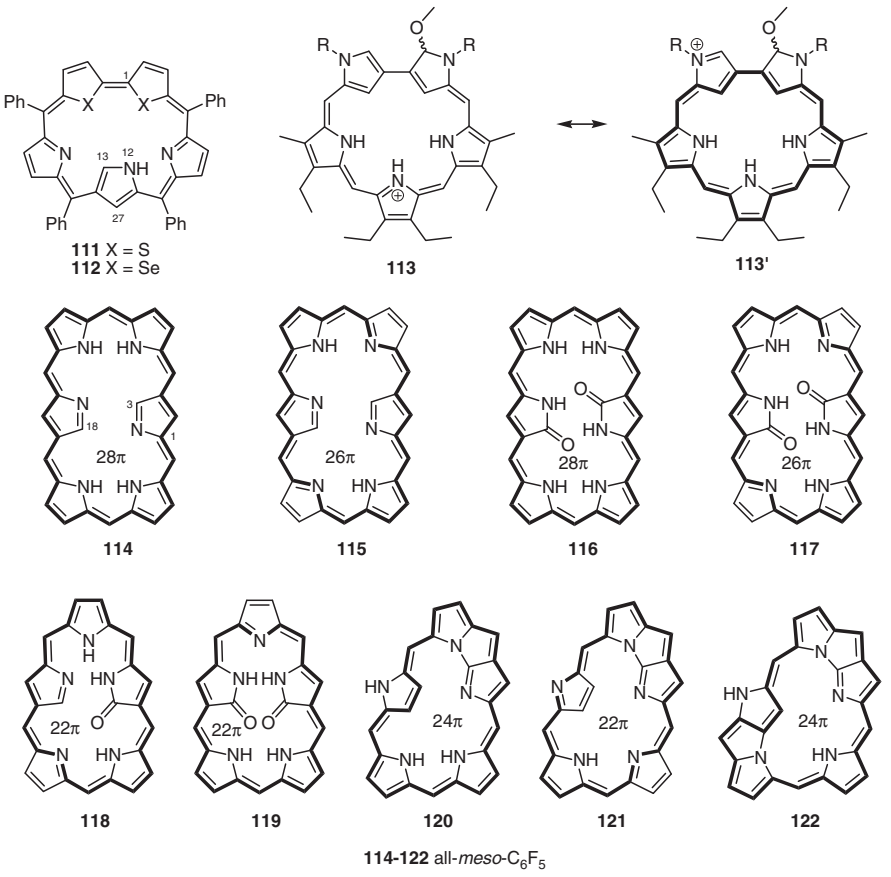


Fig. 32 Other N-confused macrocycles

The earliest examples, heterosapphyrins **111** and **112** [254], can be classified as both N-confused and inverted, because the confused pyrrole ring is permanently flipped, thus placing the "peripheral" nitrogen in the macrocyclic core. This conformation is stabilized by intramolecular hydrogen bonding, and, unlike the regular sapphyrin **48c**, compounds **111–112** were not observed to adopt an uninverted conformation. ^{1}H NMR data obtained for **111** indicate moderate diatropicity of the macrocycle ring and provide strong support for the inverted structure. Specifically, protons 12-NH, 13-H, and 27-H resonate at 5.14, 2.73, and 9.79 ppm, respectively, corresponding to their reversed positions relative to the diatropic ring current.

In a later synthetic effort, a doubly N-confused sapphyrin **113** was obtained, wherein both confused rings belong to the bipyrrolic fragment of the macrocycle [255]. In this system, a methoxy group is attached to one of the external α-pyrrolic positions, creating a peripheral sp^3 center. This structural feature, which is presumably due to spontaneous addition of a methanol molecule during the synthesis,

apparently helps in partial aromatization of the macrocycle, as discussed for other ring-confused systems. Indeed, sapphyrin **113**, exhibits a modest diatropic ring current reminiscent of doubly N-confused porphyrin **95** and thiacarbaporphyrin **100**. Likewise, the residual diatropicity was rationalized in terms of the charge-separated structure **113′**, which includes a [22]annulenoid circuit. In subsequent work, the borderline aromaticity of **113** was reinvestigated using two-photon absorption (TPA) measurements and bidirectional NICS scans [256].

Reactivity traits characteristic of N-confused porphyrin, namely ring fusion and α-pyrrolic substitution/oxidation, were also identified in N-confused penta- and hexaphyrins [257–259]. For instance, hexaphyrins **114** and **115** were observed to easily undergo oxidation at positions 3 and 18 yielding double lactams **116** and **117**, similar to **98** [257]. Compounds **114** (**116**) and **115** (**117**) possess respectively 28-π and 26-π electron conjugation pathways, and are thus related by a formal two-electron redox process. However, while **115** and **117** are diatropic, their reduced counterparts exhibit no macrocyclic paratropicity, presumably because of their strongly nonplanar conformation. Attempts to prepare a doubly N-confused pentaphyrin yielded two aromatic oxidized macrocycles **118** and **119**, whereas the parent system containing no keto functions could not be isolated [259]. A different behavior was observed in the synthesis of a singly N-confused pentaphyrin [258]. Again, the parent system could not be isolated, but this time a nonaromatic, singly fused pentaphyrin **120** was formed instead. **120** was susceptible to two-electron oxidation, yielding the aromatic **121**, which subsequently isomerized to the doubly fused system **122**. The latter molecule is of interest because the second N-fusion takes place at an unconfused pyrrole ring (for other examples see [260, 261]). Additionally, the isomerization changes the length of the conjugation pathway, creating an antiaromatic system.

3.3 Carbaporphyrins

3.3.1 "True" Carbaporphyrins and Benzocarbaporphyrins

Porphyrinoids possessing a five-membered carbocyclic ring in place of one of the pyrroles, represented by the generalized structure **123**, have been dubbed "true" carbaporphyrins to distinguish them from ring-confused systems (containing peripheral heteroatoms) and other carbaporphyrinoids containing rings larger than five-membered [7]. A number of such systems are known (Fig. 33), including substituted 21-carbaporphyrins (**124**–**125**) [262–264], carbachlorins (**126**–**127**) [265], and benzocarbaporphyrins (**128**–**130**) [263]. These systems generally preserve the [18]annulenoid aromatic character of porphyrins, which can be inferred from their ^{1}H NMR spectra. By examining allylic couplings (**131**) in a number of appropriately substituted benzocarbaporphyrins, it was shown that tautomer **123** and the corresponding valence structure are preferred in these systems, and that the C(12)–C(13) bond is largely isolated from the conjugation pathway [266]. A few other

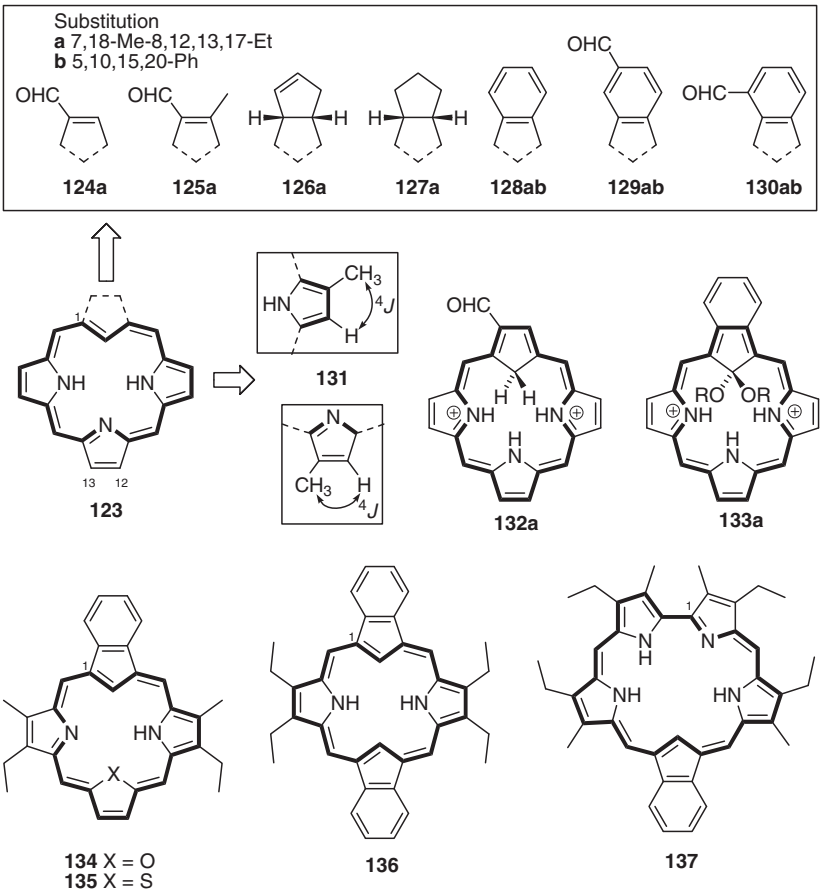


Fig. 33 Carbaporphyrins

aromatic carbaporphyrinoids were synthesized, such as heterobenzocarbaporphyrins **134**–**135** [267], bis(benzocarba)porphyrin **136** [268] (see [269] for a recent synthesis of the *adj* isomer of **136**), and benzocarbasapphyrin **137** [270].

Protonation of carbaporphyrins occurs stepwise, the first proton adding to one of the core nitrogens. The second protonation step occurs at the internal carbon, such as in **132a**, creating an sp^3 center in the macrocyclic core [264]. The ^{1}H NMR spectra show that such species are diatropic. This observation is consistent with an [18]annulenoid pathway different from that present in the free base **124a**. While the latter isolates the C(12)–C(13) bond and the peripheral part of the carbocyclic subunit, the pathway in **132a** isolates the C(7)–C(8) and C(17)–C(18) bonds while enclosing the inner tetrahedral carbon. A similar structure is found in the benzocarbaporphyrin ketal **133a** obtained by selective oxidation of **128a** [271].

3.3.2 Azuliporphyrins

Azuliporphyrins **138ab** (Fig. 34) [272–274], which contain an azulene ring incorporated in the standard porphyrinoid framework, differ significantly from the carbaporphyrins described in the previous section, even though both classes of macrocycle feature a five-membered carbocyclic ring anchored in the macrocycle in a similar fashion. This difference arises because in their basic valence formulation azuliporphyrins are cross-conjugated and contain an isolated 10-π electron system of azulene. However, ^{1}H NMR spectra indicate that azuliporphyrins are weakly diatropic, thus resembling X-confused heteroporphyrins (Sect. 3.2.4). The explanation of this residual aromaticity invokes the dipolar structure **138′**, in which the negative charge is

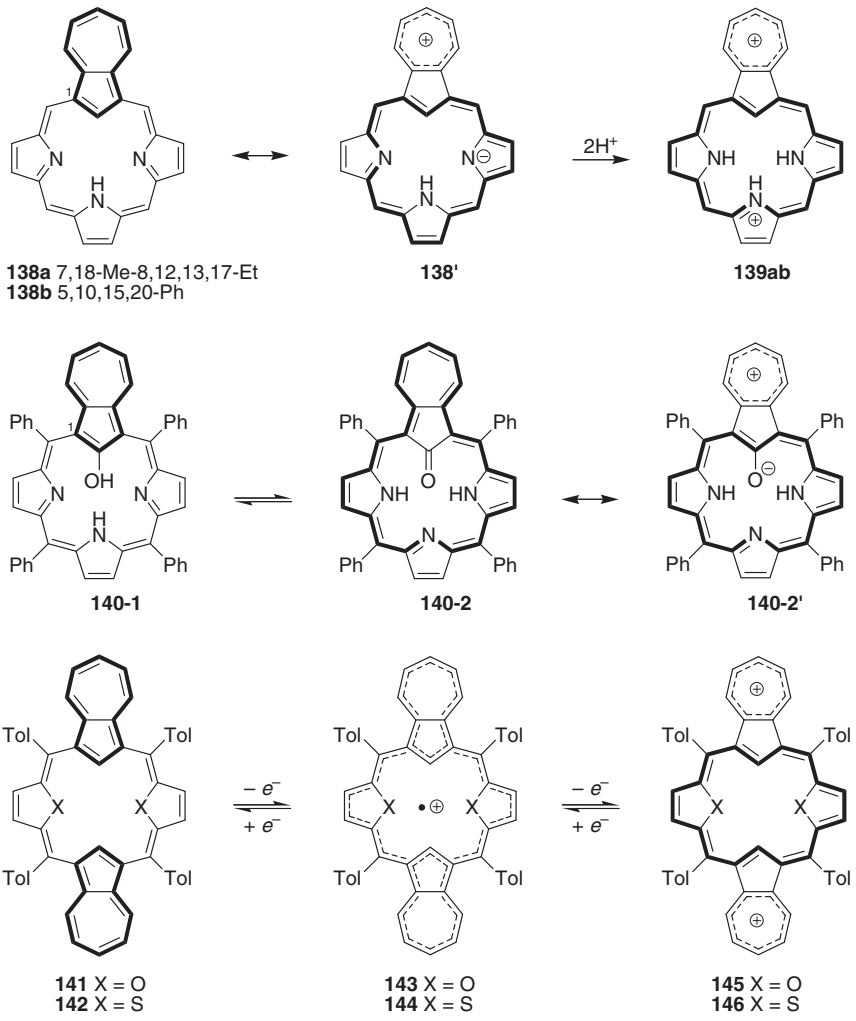


Fig. 34 Azuliporphyrins

distributed over the macrocyclic ring, whereas the positive charge resides in the seven-membered ring of azulene, which thus acquires a certain tropylium character. This contribution is even more important in the azuliporphyrin dication **139**, which is more strongly diatropic than the free base. For instance, on moving from **138a** to **139a**, the inner CH signal shifts from 1.59 to −2.56 ppm. Additionally, there is a noticeable increase in the intensity of the Soret band on protonation.

An interesting derivative, 22-oxyazuliporphyrin **140**, was obtained by selective oxidation of **138b** at the internal carbon [275]. While the prototropic tautomerism in this system was not investigated in detail, it was concluded on the basis of NMR and IR spectroscopic data that the oxy tautomer **140-2** is preferred to the hydroxy form **140-1**. Indeed, the ^{1}H NMR signature of **140-2** was different from that of **138b** and contained no particular indications of either dia- or paratropicity. Interestingly, tautomer **140-2** possesses a formal 24-π electron circuit in its basic valence form, which is contrasted with the 18-π electron circuit available in the dipolar canonical structure **140-2'**. The apparent lack of a ring current in **140** may therefore result from a cancellation of dia- and paratropic contributions or, alternatively, from insufficient overlap of p_z orbitals caused by nonplanarity of the macrocycle. This "magnetic ambiguity" is removed in the dication of **140**, which shows a fairly strong diatropic ring current, comparable with that in **139b**.

A single azulene ring was also incorporated into a variety of mixed carbaporphyrinoid systems, wherein it reduced macrocyclic aromaticity in a similar way as in tripyrrolic azuliporphyrins [276–278]. Combining the effect of two azulene moieties in a macrocyclic structure furnishes systems such as **141** and **142**, in which diatropicity is experimentally unobservable [279, 280]. Clearly, resonance contributions with double charge separation, necessary for diatropicity, are very unlikely here. Diazuliporphyrins **141** (**142**) are easily and reversibly oxidized, yielding mono- and dicationic species **143** (**144**) and **145** (**146**). Each oxidation step is associated with a marked change of the electronic spectrum, which makes these systems potential electrochromic materials. The monocations **143**–**144** are extensively conjugated organic radicals, precluding investigation of their aromatic properties using NMR spectroscopy. The dications **145**–**146** are closed-shell systems with marked diatropicity. They can be pictured as neutral diheterodicarbaporphyrins containing two tropylium cations fused with the carbocyclic five-membered rings. Such a formulation separates the 18-electron aromatic circuit of the macrocycle from the sextets of two cycloheptatrienyl cations.

4 Systems Containing Six-Membered and Larger Rings

4.1 Benziporphyrins

4.1.1 Benziporphyrin Isomers

The concept of pyrrole replacement, which has engendered hetero- and carbaporphyrinoids described above, can be extended to encompass systems containing rings larger than five-membered. A particularly important example of such a modification

is provided by benziporphyrins, in which one of the pyrrole rings is replaced with a benzene (phenylene) ring [13, 281]. These systems are not only interesting from the point of view of aromaticity and tautomerism but also because of their coordinating abilities. Benziporphyrins, whose organometallic chemistry provides examples of arene activation [282] and weak metal–arene bonding [283], can be considered macrocyclic equivalents of phenylene-based pincer ligands (see for instance [284, 285]).

The phenylene ring can be anchored in a macrocyclic structure in three distinct ways, two of which have been realized by synthesis. The corresponding systems, known as *meta*-benziporphyrin **147** [281, 282] and *para*-benziporphyrin **150** [286], are strikingly dissimilar in spite of their obvious structural relationship. In the *meta* isomer, the benzene ring is not conjugated with the macrocyclic frame, resulting in a structure that is only locally aromatic. For instance, the inner CH and NH resonances of **147b** are found at 7.33 and 10.29 ppm, respectively, confirming the absence of macrocyclic diatropicity. The electronic spectrum of **147b**, characterized by relatively low absorbance in the Soret region, is quite similar to the spectra of weakly aromatic systems such as **100**. The absence of macrocyclic aromaticity has an effect on the reactivity of *meta*-benziporphyrins. For instance, **147b** undergoes facile reduction to benziphlorin **148b** and produces hydroxybenziphlorin **149b** upon addition of a water molecule [282].

In contrast, *para*-benziporphyrin **150b** is an aromatic macrocycle and exhibits a macrocyclic ring current, which can be inferred from the positions of β-pyrrolic signals (7.7–8.2 ppm) [286]. Variable-temperature ^{1}H NMR data showed that the *p*-phenylene ring in **150b** librates in the macrocyclic frame in a seesaw fashion, a process that can be viewed as a degenerate case of ring inversion. In the fast exchange limit (323 K) one signal corresponding to the phenylene protons was observed at 5.24 ppm. Upon lowering the temperature, the signal gradually broadened and finally decoalesced into two resonances with markedly different chemical shifts (7.68 and 2.32 ppm at 168 K). This shift difference, unusual for protons attached to a single benzene ring, is readily interpreted as an additional indication of macrocyclic diatropicity. It further implies that, in the equilibrium conformation of **150b**, the phenylene ring is not perpendicular to the macrocyclic plane but tilted, so as to enhance the overlap of *p* orbitals. Such a tilt is also necessary to place the two edges of phenylene in different zones of the anisotropy cone (shielding and deshielding) thus creating the observed difference of chemical shifts. Solid-state structures of several *p*-benziporphyrin derivatives, obtained from X-ray crystallographic analyses, revealed that the angle between the phenylene ring and the plane of three N atoms takes an approximately constant value of about 45°.

para-Benziporphyrin is a showcase example of type **C** delocalization, as defined in Sect. 2.1. The resonance can be described in terms of two Kekulé structures **150-II** and **150-III** supplemented with a quinoidal structure **150-I**. Pairwise combinations of these three canonical forms correspond to three possible annulenoid circuits, one of which describes the local aromaticity of benzene, whereas the other two represent macrocyclic delocalization (Fig. 35). Thus local and macrocyclic aromaticity may be thought to coexist in *para*-benziporphyrin. Macrocyclic delocalization pathways are not possible in *meta*-benziporphyrin, for which no quinone-like structure can be drawn. Interestingly, DFT calculations predict that the *para*-benziporphyrin macrocycle **150c** is destabilized by ca. 13 kcal mol^{-1} relative to its *meta* isomer. Apparently,

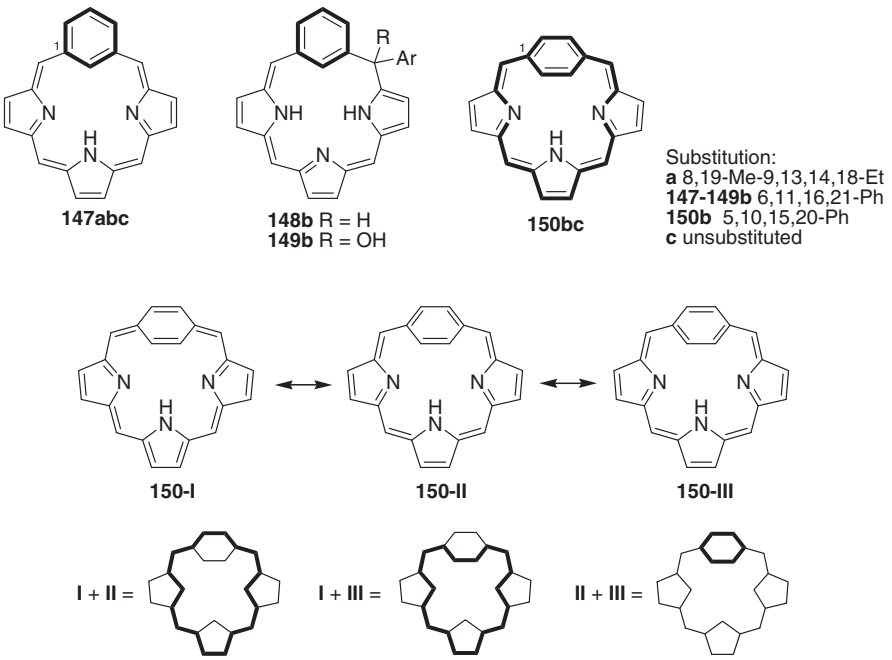


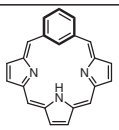
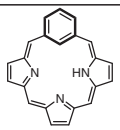
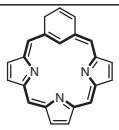
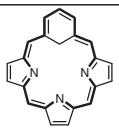
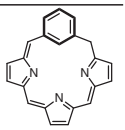
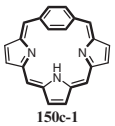
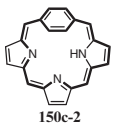
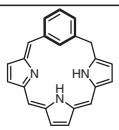
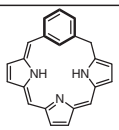
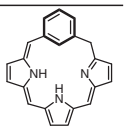
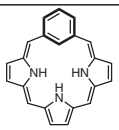
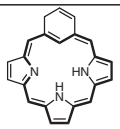
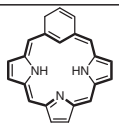
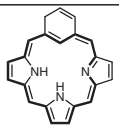
Fig. 35 Benziporphyrins

the energetic advantage offered by macrocyclic aromaticity is outweighed by the effects of strain and steric congestion, which are fairly pronounced in **150c**.

While tautomeric equilibria were not observed experimentally for *m*-benziporphyrins, it was of theoretical interest to consider potential tautomers of **147c**, including those in which protonation occurs on selected carbon atoms (**147c-1** through **147c-5**, Table 1). DFT calculations on these tautomers yielded geometries that were consistent with the expected conjugation patterns (Table 1; see Fig. 36 for an explanation of the σ parameters) [287]. For instance, marked averaging of bond lengths was observed along the [18]annulenoid pathway in **147c-4**, consistent with the expected macrocyclic aromaticity. Importantly, this structure has a much higher energy than the experimentally observed tautomer **147c-1**, showing that the aromatic stabilization of the macrocycle in **147c-4** does not compensate for the disruption of the benzene aromatic sextet. Furthermore, the potentially antiaromatic **147c-3** had an even higher energy, and its 16-π electron circuit exhibited strong bond length alternation. Finally, structure **147c-5**, which contains a tetrahedral *meso* carbon and can be called "benziisoporphyrin," is also destabilized relative to **147c-1**.

A similar analysis carried out on the doubly reduced *m*-benziporphyrin (benziphlorin, **148c**) showed that also in this case the aromatic sextet of the benzene ring is preferred over 18-π electron macrocyclic aromaticity, as evident from the energy difference of over 11 kcal mol^{-1} between **148c-6** and **148c-2**. In addition, the "benziisophlorin" structure **148c-4** was also found to have a higher energy, possibly because of the in-core steric repulsion of four hydrogen atoms.

Table 1 Energies and delocalization parameters for selected tautomers of *m*-benziporphyrin (**147c**) and *m*-benziporphyrin (**150c**), and *m*-benziphlorin (**148c**)

					
	147c-1	**147c-2**	**147c-3**	**147c-4**	**147c-5**
E	0.00	7.19	58.42	41.25	35.75
σ(meso)	3.3	3.2	4.0	**0.0**	–
$\sigma(C_5)$	2.1	2.1	4.5	–	–
$\sigma(C_7)$	2.5	2.4	–	**0.4**	–
$\sigma(C_6)$	**1.0**	**1.1**	–	–	**1.0**
					
	150c-1	**150c-2**	**148c-1**	**148c-2**	**148c-3**
E	12.70	18.93	5.71	0.00	4.06
σ(meso)	1.6	1.6	–	–	–
$\sigma(C_5)$	–	–	–	–	–
$\sigma(C_7)$	–	–	–	–	–
$\sigma(C_6)$	2.2	2.2	**0.8**	**0.7**	**0.7**
					
	148c-4	**148c-5**	**148c-6**	**148c-7**	
E	10.86	15.24	11.30	15.12	
σ(meso)	3.9	**0.4**	**0.7**	**0.8**	
$\sigma(C_5)$	2.3	**0.7**	**0.9**	**0.9**	
$\sigma(C_7)$	2.7	–	–	–	
$\sigma(C_6)$	**1.0**	–	–	–	

DFT calculations were performed at the B3LYP/6-31G*//B3LYP/6-31G** level of theory [287]

[a]Energies (*E*) are in kcal mol^{-1} and are given relative to **147c-1** (**147c-*n*** and **150c-*n***) and **148c-2** (**148c-*n***)

[b]σ values are given in picometers; values corresponding to paths containing sp^3 carbons were omitted; values lower than 1.5 pm are shown in bold

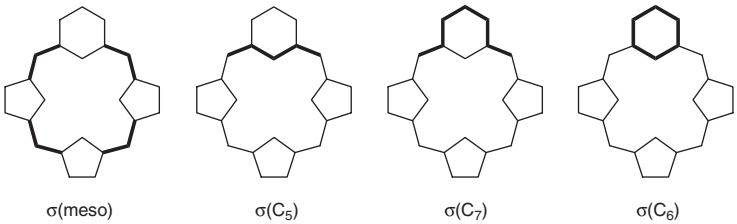
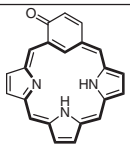
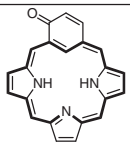
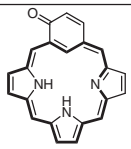
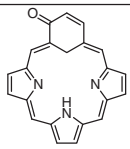
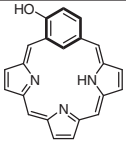
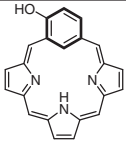
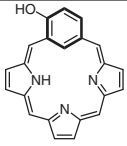
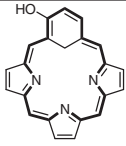
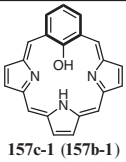
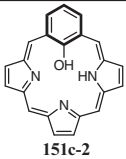
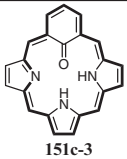
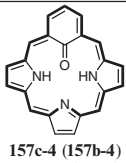
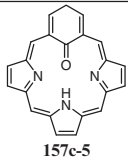


Fig. 36 Definition of parameters σ used in Tables 1 and 2. Each σ value is a root mean square deviation calculated for the set of C–C bond lengths shown in *bold*. Low σ values (<1.5 pm) are indicative of bond length averaging. The expected value for an alternating pattern of pure single and double bonds is ca. 6 pm [287]

4.1.2 Hydroxybenziporphyrins

The potential of the *m*-benziporphyrin skeleton to produce aromatic macrocycles, foreseeable in the above discussion of its hypothetical tautomers, was actually revealed by introduction of hydroxy groups on the phenylene ring. These functionalities serve as additional tautomerization sites, which become effective aromaticity switches in appropriately designed systems. Theoretical insight into the switching capabilities of hydroxybenziporphyrins was gained from a theoretical survey of relative stabilities and aromatic character of various hydroxybenziporphyrin tautomers [287, 288], which was concurrently verified by experimental work (Table 2) [250].

Table 2 Energies and delocalization parameters for selected tautomers of 2-hydroxybenziporphyrin (**151c**) and 22-hydroxybenziporphyrin (**157c**)

					
	151c-1	**151c-2**	**151c-3**	**151c-4**	
E	4.72	0.00	3.81	18.10	
σ(meso)	**0.8**	**0.7**	**0.9**	2.5	
$\sigma(C_5)$	**0.6**	**0.5**	**0.5**	–	
$\sigma(C_7)$	4.9	4.9	4.9	5.4	
$\sigma(C_6)$	5.0	5.0	5.8	–	
					
	151c-5	**151c-6**	**151c-7**	**151c-8**	
E	20.26	12.80	20.25	54.70	
σ(meso)	2.8	3.0	2.8	0.4	
$\sigma(C_5)$	1.8	1.8	1.9	–	
$\sigma(C_7)$	2.3	2.3	2.3	1.0	
$\sigma(C_6)$	1.4	1.4	1.4	–	
					
	157c-1 (157b-1)	**151c-2**	**151c-3**	**157c-4 (157b-4)**	**157c-5**
E	0.00 (0.00)	16.95	0.02	–8.34 (–3.35)	30.48
σ(meso)	3.3	2.2	2.7	2.2	3.7
$\sigma(C_5)$	**1.2**	**0.9**	1.9	**0.9**[c]	2.5
$\sigma(C_7)$	2.6	1.8	2.1	1.9	–
$\sigma(C_6)$	1.6	2.7	3.3	2.7	–

Geometry optimizations were performed at the B3LYP/6-31G* level of theory for **151c** [250] and at the B3LYP/6-31G** level for **157c** [288]

[a]Energies (*E*, B3LYP/6-31G**) are in kcal mol^{-1} and are given relative to **151c-2** (for **151c-*n***) and **157c-1** (for **157c-*n***)

[b]σ values (B3LYP/6-31G* geometries for both **151c-*n*** and **157c-*n***) are given in picometers; values corresponding to paths containing sp^3 carbons were omitted; values lower than 1.5 pm are shown in bold [287]

[c]This value is accidentally low (all four bonds are elongated to similar extent).

The first such system, 2-hydroxybenziporhyrin **151a** (Fig. 37), was found to completely tautomerize to the aromatic keto species **151a-2**, named 2-oxybenziporphyrin [289, 290]. The latter form, which displays the full characteristics of an aromatic macrocycle, is preferred over the hydroxy tautomer, in which aromaticity would be restricted to the benzene ring. **151a** is initially protonated on the free internal nitrogen, yielding an aromatic monocation **152a**. In more acidic media, a dication of **153a** is observed, which is additionally protonated at the external oxygen. Consequently, the dication adopts a phenol-like electronic structure, which results in an observable reduction of macrocyclic diatropicity.

The tautomeric preferences of **151a** and, consequently, its aromaticity are influenced by metal coordination [250]. The monoanionic Pd complex **154a** retains the [18]annulenoid structure characteristic of the free base. However, upon addition of an electrophile (including a proton) to the external oxygen, a variety of O-substituted derivatives are formed (**155a**, R = H, alkyl, acyl), in which macrocyclic aromaticity is largely reduced. Interestingly, substitution at the internal carbon (22-C) leads to structures of type **156a** (R = Me, *n*-Bu), which retain macrocyclic conjugation in spite of apparent bonding between palladium and 22-C.

When the OH group was placed on the internal carbon of benziporphyrin, as in **157b**, the behavior of the resulting system was very different [288]. Spectroscopic

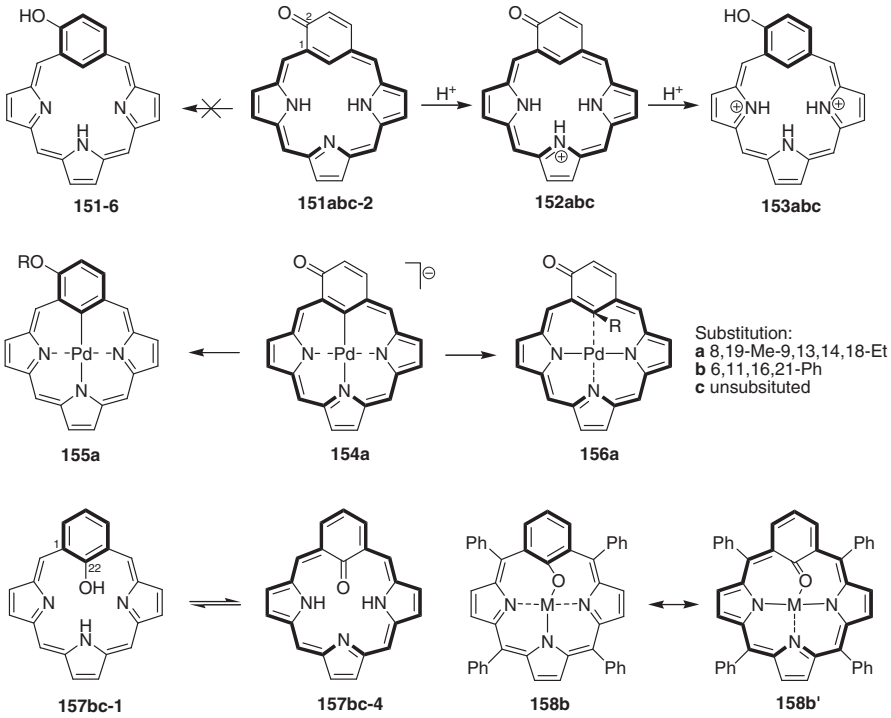


Fig. 37 Hydroxybenziporphyrins and their metal complexes

data showed that, in solution, 22-hydroxybenziporphyrin **157b-1** undergoes a very fast exchange with the 22-oxy tautomer **157b-4**. The latter contains a [20]annulenoid pathway and displays features of an antiaromatic system. The two species are present in solution at comparable concentrations, indicating that in **157b-4**, the antiaromatic destabilization is not as significant as might be expected. Indeed, DFT calculations predicted the energy of **157b-4** to be lower by -3.35 kcal mol^{-1} than that of **157b-1**. 22-Hydroxybenziporhyrin forms complexes with divalent metal ions, such as Ni(II), Pd(II), or Zn(II), in which the ion is bound by the three pyrrolic nitrogens and the phenolate donor (**158b**) [291]. These complexes display a modest paratropic ring current corresponding to the [20]annulenoid delocalization associated with the keto structure **158b**.

4.2 Pyriporphyrins

4.2.1 Pyriporphyrin Isomers

The structural paradigm found in benziporphyrins can be logically extended by replacing the phenylene fragment with a heteroaromatic six-membered ring such as pyridine. The lower symmetry of the pyridine ring, compared with that of benzene, leads to an increased number of distinct anchoring modes, which differ not only in the separation of attachment points (e.g., *meta* vs. *para*) but also in the position of the nitrogen atom. For instance, three isomers of *meta*-pyriporphyrin are possible that do not contain a bridgehead nitrogen atom. In spite of the synthetic difficulties imposed by the basic pyridine ring, all three isomers **159**, **161**, and **163** (Fig. 38) were eventually prepared and characterized [292–295] (an early attempt to synthesize **159** is described in [296]).

22-Aza-*meta*-benziporphyrins (pyriporphyrins) **159ad** do not exhibit macrocyclic aromaticity, similarly to *meta*-benziporphyrin **147**. The potentially aromatic tautomer **159a-2**, protonated on the pyridine nitrogen, was not observed experimentally and DFT calculations indicated that it should have a significantly higher energy (18 kcal mol^{-1} relative to **159a-1** at the B3LYP/6-31G** level) [294]. However, weak diatropism was observed in the ^{1}H NMR spectrum of the monocation of **160a**, which presumably exists as a mixture of tautomers **160a-1** and **160a-2**. The weakly aromatic character of the monocation, which leads to a moderately upfield shift of the NH protons (6.10 ppm; Table 3 in the Appendix lists ^{1}H NMR and UV-vis data for **160a** and other porphyrins and porphyrinoids), was explained in terms of the resonance contribution **160a-1**, which possesses an [18]annulenoid conjugation pathway. Residual diatropicity is also observed in the chlorozinc(II) complex of **159a**. Macrocyclic aromaticity is restored in 2-oxypiriporphyrin **165e**, in analogy to 2-oxybenziporphyrin [292, 297, 298].

In the other two isomers of **159**, 3-aza-*m*-benziporphyrin (**161**) and 2-aza-*m*-benziporphyrin (**163**), the aromatic character is also limited to the local aromaticity of the heterocyclic rings [293]. Interestingly, the 2-aza ring system could be

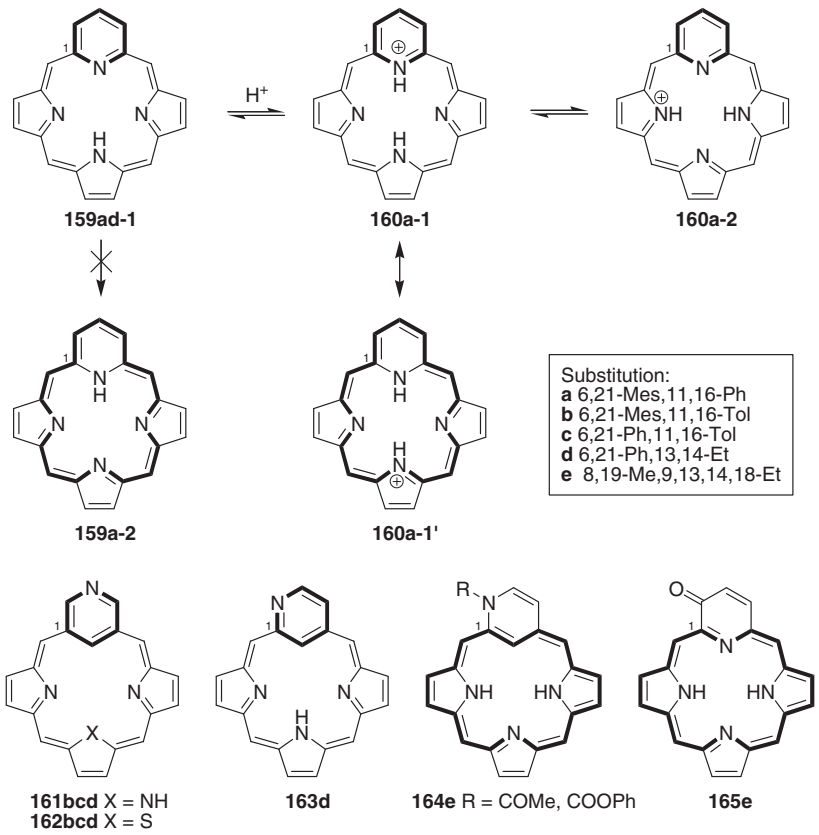


Fig. 38 Pyriporphyrins

converted into an aromatic macrocycle (**164e**) by substitution of the external nitrogen atom prior to oxidation of the porphyrinogen [295]. 3-Aza-24-thia-*m*-benziporphyrin **162** undergoes acid-catalyzed addition of water, with regioselectivity dependent on *meso* substitution (Fig. 39) [293]. In the phenyl-substituted species **162c** the hydroxy group is added to one of the *meso* positions to form a hydroxyphlorin **166c**. Interestingly, the bulky mesityl substituents in **162b** divert the reaction from the *meso* positions to the pyridine ring. The resulting species **167b**, characterized by disrupted conjugation in the pyridine unit, exhibits a macrocyclic ring current in the ^{1}H NMR spectrum.

4.2.2 Subpyriporphyrin

Subpyriporphyrin **168** (Fig. 40) is a contracted porphyrinoid containing two pyrrole and one pyridine subunit connected with three methine bridges. It can be thought

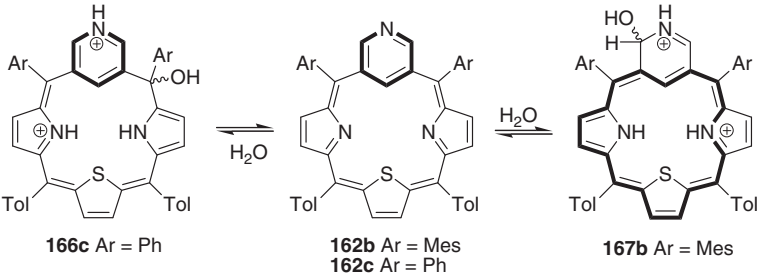


Fig. 39 Reactivity of 3-aza-24-thia-*m*-benziporphyrins towards nucleophiles

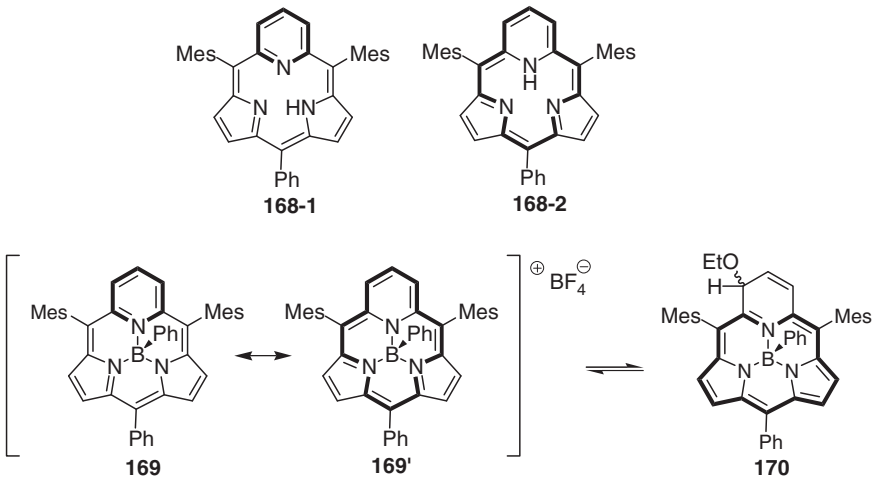


Fig. 40 Subpyriporphyrins

of as a homolog of [14]triphyrin(1.1.1) (Sect. 2.6.2), containing an additional CH unit in one of the pyrrole rings. Unlike regular triphyrins, which so far have only been obtained as boron complexes, **168** was synthesized directly as a free base [299]. Both in solution and in the solid state, subpyriporphyrin exists exclusively as tautomer **168-1**, characterized by a uniquely strong, three-centered hydrogen bond. The unobserved pyridine-protonated tautomer **168-2**, which should exhibit diatropicity due to the [14]annulenoid conjugation pathway, is 4.66 kcal mol^{-1} higher in energy than **168-1**, according to DFT calculations. The potential of subpyriporphyrin for macrocyclic aromaticity is revealed in its phenylboron complex **169**. The diatropicity of this species, resulting from the resonance contribution **169**, is most strikingly manifested by the unusually upfield shift of the *ortho* protons bound to the axially coordinated σ-phenyl ring (4.87 ppm).

Complex **169** undergoes addition of alkoxides to yield the peripherally substituted product **170** as a mixture of stereoisomers. In this system, the macrocyclic

conjugation is interrupted at the addition site, however, a different [14]annulene pathway is formed instead, which does not include the outer part of the pyridine ring. Accordingly, **169** and **170** display a similar degree of aromatic character.

4.3 Tropiporphyrins

In tropiporphyrin **171** (Fig. 41), a cycloheptatrienyl ring replaces one of the pyrroles to yield a structure with an [18]annulenoid conjugation pathway and distinct macrocyclic aromaticity [272, 300, 301]. In the presence of acids, tropiporphyrin **171a** undergoes stepwise protonation, yielding an aromatic monocation **172a** and a nonaromatic dication **173a-1**. In the latter system, macrocyclic conjugation is interrupted because the second proton is attached to one of the *meso* positions non-adjacent to the seven-membered ring [301]. The formation of **173a-1** is in contrast with the behavior of carbaporphyrins (Sect. 3.3.1), which form dications protonated on the

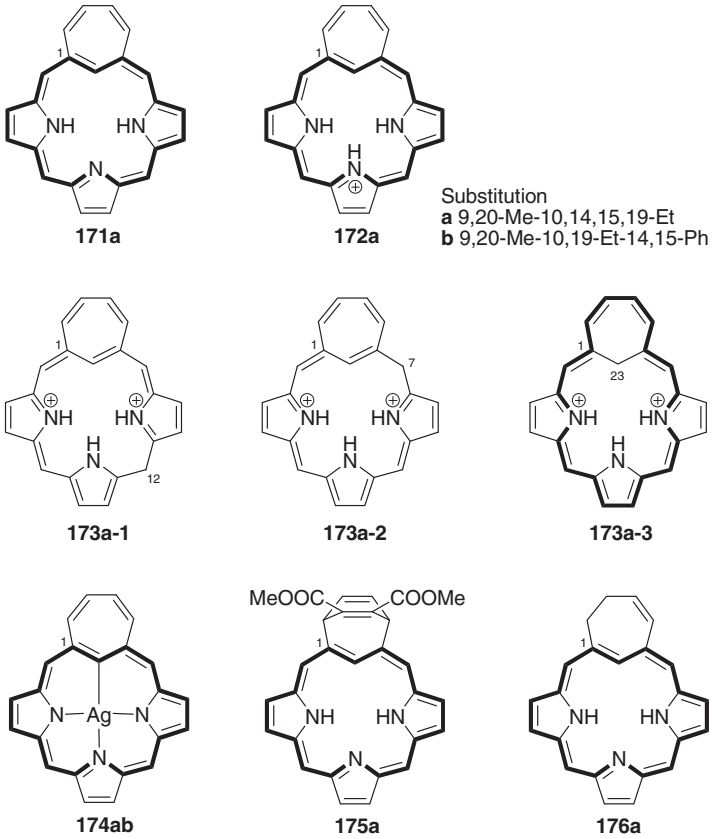


Fig. 41 Tropiporphyrins

internal carbon, but it resembles the second protonation event reported for corroles (Sect. 2.6.1). Nevertheless, as evidenced by ^{1}H NMR spectra of **171a** recorded in the presence of trifluoroacetic acid-*d*, dication **173a** is slowly deuterated at *meso* positions adjacent to the cycloheptatrienyl ring and, even more sluggishly, at the internal carbon. These observations imply that **173a-1** is in equilibrium with minute amounts of the two tautomers **173a-2** and **173a-3**. The latter species possesses a formal [20]annulenoid pathway and might in principle be antiaromatic.

The peripheral diene fragment of the cycloheptatrienyl ring is not conjugated with the rest of the macrocycle. This property of tropiporphyrins is manifested in the X-ray structure of the Ag(III) complex **174b**, which shows that the seven-membered ring is significantly twisted, with its peripheral part distorted out of the macrocyclic plane. The diene unit in **171a** is weakly reactive towards dienophiles, forming the Diels–Alder adduct **175a** (13% yield) in a reaction with dimethyl acetylenedicarboxylate (DMAD), and is susceptible to reduction with diimide to form compound **176a**. Compound **175a** exhibits a stronger ring current than the parent **171a**, which was interpreted in terms of a reduced out-of-plane distortion of the macrocycle in the former system.

5 Conclusions and Outlook

Porphyrins and porphyrinoids provide fertile ground for exploration of π-aromaticity. While many of the molecules described in this review were synthesized with the goal of creating unusual π-conjugated structures, some of them, such as the first N-confused porphyrins, were obtained through sheer serendipity. The aromaticity of porphyrinoids can be controlled by means of a number of structural modifications that are at the disposal of synthetic chemists. In particular, π-conjugation in porphyrin analogs depends on the topology of the molecular framework, conformation of the macrocycle, tautomerism, and metal coordination. Many effects, such as easily available multiple oxidation states, aromaticity switching via tautomeric equilibria, and, last but not least, Möbius-type conjugation [147–149], are more easily achieved in porphyrinoids than in other classes of π-conjugated molecules.

Given the biological relevance of porphyrins and the potential of porphyrinoids as advanced electro- and photoactive molecular materials, deep understanding of their electronic structure is of high current importance. In spite of spectacular advances in the field of porphyrinoid aromaticity, systems of significant interest can still be created, for instance by further ring expansion and contraction, extensive ring fusion, or introduction of hitherto unexplored structural elements. Considering the challenge inherent in porphyrin synthesis, such efforts are likely to engage chemists for years to come.

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Appendix

Table 3 ^{1}H NMR shift data and UV–vis data for selected porphyrins and porphyrinoids

	^{1}H NMR data[a]				UV–vis data		
Compound/conditions	Meso[b] [ppm]	β[b] [ppm]	NH[c] [ppm]	CH[c][ppm]	λ [nm]	log ε [M^{-1}cm^{-1}]	Ref.
1 (porphine)	10.58	9.74	−3.76	–	395, 490, 520, 563, 569, 616	5.42, 4.20, 3.48, 3.72, 3.64, 2.95	[33]
1a	–	8.75	−2.76	–	419, 515, 548, 592, 647	5.67, 4.27, 3.91, 3.72, 3.53	[33]
1b	10.18	–	−3.74	–	400, 498, 532, 568, 596, 622	5.20, 4.16, 4.03, 3.83, 3.18, 3.76	[33]
7a ($CDCl_3$)	7.8, 7.7, 6.9	–	nd	–	400, 586, 634	5.06, 4.03, 4.25	[78]
8a ($CDCl_3$ + TFA)	9.32, 9.12, 8.52	–	nd	–	405, 500, 537, 586, 647, 6.96	4.90, 3.56, 3.68, 3.66, 3.93, 4.22	[78]
9a-1 (TFA)	10.55, 10.47, 10.07	–	−1.90, −2.17, −2.83, −2.92	–	420, 528, 563, 618	5.42, 3.44, 3.94, 4.03	[78]
30a	9.83	9.67, 9.23	3.15	–	358, 370, 558, 596, 630	5.14, 5.03, 4.53, 4.48, 4.72	[114]
30b	9.48	–	0.65	–	385, 576, 625, 665	5.16, 4.55, 4.29, 4.49	[116]
30c	–	9.43, 9.18	6.82	–	373, 593, 645, 659	5.21, 4.33, 4.63, 4.66	[115]
37c	–	6.09, 6.02	6.94	–	220s, 278, 320s	4.37, 4.55, 4.08	[127]
38a (UV–vis in benzene)	9.24, 8.91, 8.90, 8.54	9.08, 9.03, 8.91, 8.75, 8.64, 8.54	6.45, 3.51	–	360, 382, 402, 532s, 548s, 560, 575, 595	4.85, 4.71, 4.87, 4.05, 4.18, 4.23, 4.38, 4.48	[126]
38c	–	8.80, 8.74, 8.70, 8.62, 8.50, 8.43	10.20, 6.77	–	353s, 372, 394, 415, 554s, 597, 630	4.78, 4.91, 4.73, 4.90, 4.13, 4.49, 4.42	[127]
40a (NMR in $DClO_4$)	11.30	11.46, 10.93	–	–	307, 372s, 376, 457s, 482, 512, 523s, 552, 567, 575, 587, 599, 610s, 623s	3.81, 5.53, 5.58, 2.74, 3.46, 3.72, 3.53, 4.45, 3.79, 3.31, 3.82, 4.66, 3.34, 2.45	[129]
41a (NMR in C_6D_6)	4.19	4.94, 4.90	–	–	303, 307, 317, 354s, 380s, 400s, 517	5.03, 5.03, 5.20, 3.75, 3.59, 3.19, 2.81	[129]
48b dichloride salt	11.66, 11.77	–	−4.31, −4.64, −4.97	–	456, 624, 676	5.71, 4.07, 4.15	[156]

48c-2 (CD_2Cl_2, 203 K)	–	10.16, 9.20, 9.02, 9.15, –1.50	–2.58, 12.24	–	395, 493, 518, 640, 697, 795	4.01, 4.87, 4.77, 3.66, 4.02, 3.73	[154]
51a	–	–	0.64	–	431, 1112	4.90, 5.12	[165]
53a	–	–	–2.12	–	429, 936	4.65, 4.82	[166]
54a	–	–	–1.34	–	397, 708, 792	5.09, nd, 5.31	[166]
55a	–	–	–	–	387, 439, 643	4.50, 4.40, 4.41	[170]
56a	–	9.10, 8.75, 8.57	–2.25	–	408, 560, 602	5.06, 4.25, 3.97	[173]
56b (UV–vis)	9.12, 8.82	–	–3.48	–	346, 408, 474, 502, 525	4.22, 5.00, 3.52, 3.83, 3.92	[171]
56c (NMR)							
59b (NMR in FSO_3H, UV–vis in H_2SO_4)	8.06, 7.96, 4.7 (2H, CH_2)	–	9.07, 8.25, 6.47	–	292, 358, 671	4.29, 4.70, 4.46	[178]
88b	–	8.99, 8.92, 8.61, 8.58, 8.58, 8.56	–2.56, –2.67	–5.08	440, 506, 543, 585, 672, 730	4.99, 3.67, 3.87, 4.04, 3.45, 3.99	[220]
88a	–	nd	–2.41	–4.99	nd	nd	[225]
88a-2 (in DMF-d_7)	–	nd	2.27	0.76			[225]
88c	10.1, 9.70, 9.56, 9.54	–	–3.87	–6.30	352, 420, 515, 552, 618, 681	4.52, 5.12, 4.11, 3.87, 3.38, 3.56	[223]
88d	10.33, 10.03, 9.92, 9.85	9.45, 9.39, 9.27, 9.26, 9.22, 9.19	–3.70	–6.42	331, 413, 506, 680	4.51, 5.11, 4.15, 3.52	[224]
88d in DMF	nd	nd	nd	nd	331, 417, 456, 565, 608, 653	4.53, 4.95, 4.26, 3.77, 3.81, 3.75	[224]
89a	–	7.96, 7.85, 7.78, 7.77, 7.52, 7.48	3.43	0.98	450, 660, 710	4.94, 4.01, 4.11	[228]
95	–	7.36, 7.28, 7.06, 6.98, 6.94, 6.40	6.40	3.52, 3.22	347, 424, 628, 668	4.61, 4.67, 4.04, 4.00	[235]
96	–	8.85, 8.57, 8.44 (overlapping)	–2.73, –3.21	–4.34, –4.36	359, 449, 554, 602, 776	4.54, 5.10, 4.00, 3.95, 3.78	[238]
97	–	8.50–7.83	–	–	337, 448, 490, 528, 578, 784	4.60, 4.15, 4.11, 3.78, 3.70, 3.85	[238]
100	–	7.53, 7.52, 7.40, 7.40, 7.20, 7.16	5.81	4.76	437, 705s, 763s	4.97, nd, nd	[245]

(continued)

Table 3 (continued)

Compound/conditions	^{1}H NMR data[a]				UV–vis data		Ref.
	Meso[b] [ppm]	β[b] [ppm]	NH[c] [ppm]	CH[c] [ppm]	λ [nm]	log ε [$M^{-1}cm^{-1}$]	
101 (dication)	–	8.32, 8.27, 7.85, 7.82, 7.82, 7.79	5.32, 5.10, 4.37	1.32	335, 412, 445, 472, 576, 624, 685, 807, 907	4.34, 4.43, 4.63, 4.90, 3.84, 3.90, 3.94, 3.89, 4.09	[246]
102	–	8.68, 8.61, 8.58, 8.58, 8.57, 8.57	–3.37, –2.93	–5.31	443, 533, 575, 635, 696	5.01, 4.09, 3.90, 3.82, 3.78	[245]
106	–	7.85, 7.80, ~7.6, ~7.6, 7.48, 7.39	4.47	2.39	360, 420, 449, 502, 528, 627, 681, 809, 883	4.04, 4.18, 4.15, 4.17, s, 3.46, 3.77, 3.29, 3.17	[247]
107	–	4.61, 8.33, ~7.8–7.9	nd	–0.51	356, 389, 444, 472, 533, 573, 652, 708, 911	3.91, 3.98, 4.17, 4.13, 4.11, 4.18, 3.58, 3.52, 3.39	[247]
109e (Ar = Tol)	–	9.06–7.60	8.48	–	359, 499, 545, 648, 705, 855, 941	4.62, 4.70, 4.54, 3.81, 3.63, 3.46, 3.53	[249]
124a (*meso* shifts include 3-H and CHO signals)	10.69, 10.66, 9.48, 9.46, 9.40, 8.60	–	–3.80	–6.80	364, 436, 524, 566, 640, 710	4.67, 4.99, 4.09, 4.18, 3.42, 3.50	[264]
132a (50% TFA) (*meso* shifts include 3-H and CHO signals)	12.12, 11.92, 11.60, 11.50, 11.05, 10.99	–	–3.67	–7.42	410, 426, 548, 600, 664	5.16, 5.02, 3.79, 4.07, 3.50	[264]
138a (pyridine-d_5)	8.64, 9.55	–	nd	1.59	354, 396, 444, 472, 622, 658	4.78, 4.69, 4.70, 4.81, 4.16, 4.16	[273]
139a (+TFA)	9.42, 10.32	–	nd	–2.56	364, 460, 592, 638, 678, 734	4.95, 5.08, 3.85, 4.46, 4.17, 3.82	[273]
147a	6.57, 6.27	–	8.93	7.90	317, 384, 620, 663, 720	4.72, 4.83, 3.70, 3.78, 3.60	[281]
147b	–	6.52, 6.74, 7.19	10.29	7.33	319, 411, 723	4.53, 4.89, 4.09	[282]
150b (323 K, $CDCl_3$)	–	7.62, 7.74, 8.20	1.26	–	431, 600	5.10, 4.69	[286]
150b (168 K, CD_2Cl_2)	–	7.68*	nd	2.32*			[286]
159a	–	7.03, 6.94, 6.66	9.38	–	324, 411, 685	4.46, 4.61, 4.00	[294]

160a	–	7.68, 7.59, 7.55	6.10	–	nd		[294]
161b	–	6.78, 6.67, 6.57	10.43	8.30	325, 410, 730	4.60, 4.68, 3.94	[293]
164e (R = COOPh)	9.56, 9.49, 9.37, 8.53	–	nd	–6.66	420, 495, 530, 567, 644, 709	4.86, 3.76s, 3.90, 4.13, 3.61, 3.93	[295]
167b	–	9.23, 9.20, 8.22, 8.21, 8.02, 7.97	1.80, 1.75	–3.36	nd		[293]
168	–	7.41, 7.18	17.82	–	346, 730	4.40, 3.71	[299]
169	–	8.07, 7.85	–	–	358, 485, 523, 687	4.46, 3.54, 3.43, 3.85	[299]
170 (NMR for *syn* isomer UV–vis for *syn/anti* mixture)	–	8.03, 7.98, 7.34, 7.29	–	–	365, 382, 530	4.61, 4.75, 4.34	[299]
171a	9.22, 8.02	–	nd	–7.45	348, 402s, 439, 569, 619	4.45, 4.70, 4.88, 3.90, 4.26	[301]
176a	9.86, 9.47	–	nd	–9.17	408, 497, 533, 592, 649	5.09, 4.06, 3.59, 3.41, 3.69	[301]

Where necessary, measurement conditions are indicated nd no numerical data available, s shoulder (inflection)

[a]Where necessary chemical shifts were converted from the τ scale

[b]Meso and β shifts are given for sp^2 centers

[c]NH and CH correspond to shifts of the inner protons bound to nitrogen or carbon

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How Aromaticity Affects the Chemical and Physicochemical Properties of Heterocycles: A Computational Approach

I. Alkorta and J. Elguero

Abstract Our publications dealing with problems related to aromatic heterocycles are discussed with the appropriate references from the literature. The three main topics are theoretical calculations, tautomerism, and NMR spectroscopy but other aspects are also discussed, such as crystal structures, proton transfer, hydrogen bonds, IR, etc.

Keywords Heteroaromaticity, Hydrogen bonds, NMR, Proton transfer, Tautomerism

Contents

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1 Introduction

1.1 Aromaticity

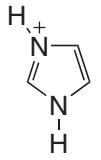
Aromaticity is one of the great unifying principles of chemistry and although it was devised for benzene and other hydrocarbons it was soon extended to heterocycles. For instance, the Hückel rule was published in 1931 [1, 2], while Robinson introduced the aromatic sextet concept in 1925 [3–5] and extended it to five-membered heterocycles, considering that a C–C double bond can be replaced by an heteroatom bearing a lone pair [3–5] (see however [6]). In this review we will discuss only heteroaromaticity, leaving aside most aspects concerning aromaticity. Even so, the number of literature references is enormous so we will restrict ourselves to our own contributions and to some recent and important papers by others.

It is clear, as Katritzky et al. [7, 8] and ourselves [9] have pointed out, that aromaticity cannot be described with a single parameter. It is possible to select a parameter and classify aromatic compounds according to it and this approach is correct if one bears in mind that the aromaticity scale thus obtained is valid only for the chosen parameter. One of the most successful is Schleyer's NICS (nuclear independent chemical shifts) [10–12], a criterion we have used to separate aromatic and antiaromatic compounds [13]. Cyranski et al. [14] as well as Sadlej-Sosnowska [15] have tried, with moderate success, to find an agreement between these different points of view.

1.2 Heteroaromaticity

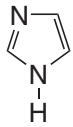
Many papers (see, for instance [16, 17]) and some books [18] have been devoted to discussion of the aromaticity of heterocycles. However, a simple problem such as knowing where the imidazolium cation (**1**) and imidazolate anion (**2**) are more or less aromatic than imidazole itself (**3**) is not solved, and probably never will be because it depends on the chosen aromaticity criteria. The NICS(1) values (NICS at 1 Å above the ring plane, calculated at the GIAO//B3LYP/6-311++G** level) are

shown below (benzene = –10.23 ppm). The aromaticity of azoles and benzazoles has been discussed by several authors, including Krygowski et al. [19] and Karolak-Wojciechowska et al. [20, 21].



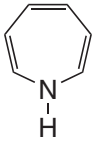
1
–10.13 ppm

2
–10.97 ppm



3
–10.57 ppm

We have introduced the concept of homoheteroaromaticity (the equivalent of homoaromaticity [18] for heterocycles) to describe the structure of some cations obtained by protonation of 1*H*-azepine (**4**) and 5*H*-dibenz[*b*,*f*]azepine (**5**). B3LYP/6-311++G**, GIAO, and NICS calculations together with some NMR experiments lead us to conclude that the neutral molecules are antiaromatic and that the cations **6** and **7** are homoaromatic [22].



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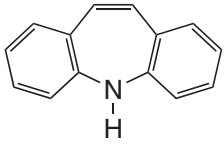

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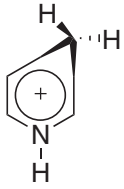

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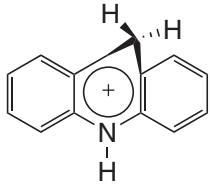

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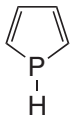
We have used a different approach to compare the aromaticities of phosphole (**8**) and pyrrole (**10**) [23, 24]. From literature data on derivatives of **8** and **9** it is known that the inversion barrier of phosphole is about 67 kJ mol^{-1} (70.2 kJ mol^{-1} at the B3LYP/aug-cc-pVTZ level) [25] while that of tetrahydrophosphole amounts to 163 kJ mol^{-1}. This is explained by the fact that the planar transition state of **8** is highly aromatic. Pyrrole (**10**) is planar and pyrrolidine has a calculated inversion barrier of 15–17 kJ mol^{-1}. Several aromaticity indices were used in this study, based on different criteria of aromaticity: energetic (aromatic stabilization energy, ASE), geometric (harmonic oscillator model of aromaticity, HOMA, and I_5), and magnetic (NICS).



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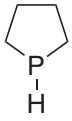

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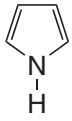

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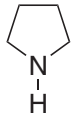

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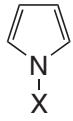

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In a subsequent paper [26], we studied theoretically the X substitution effects on the aromaticity of phenyl and *N*-pyrrole derivatives (**12**) along the periodic table [X = H, Li, BeH, BH_2, CH_3, NH_2, OH, F, Na, MgH, AlH_2, SiH_3, PH_2, SH, Cl]. The analysis was carried out by means of the atoms in molecules (AIM) methodology using the electron density obtained through B3LYP/6-31+G(d,p) DFT calculations. The results have been rationalized, based on the electronegativity of the substituents. In addition, the different parameters obtained have been correlated with different aromaticity indexes (HOMA, NICS, and ASE). The results obtained with the AIM methodology show good relationships with Pauling's electronegativity of the substituents.

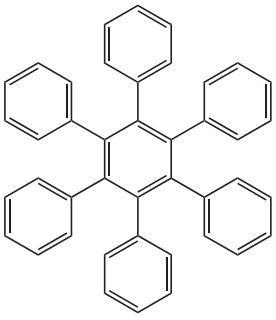
2 Aromatic Heterocycles

We will discuss aromatic heterocycles in the following order: ground-state properties (Sect. 3), reactivity (Sect. 4), spectroscopy (Sect. 5), special heterocycles (Sect. 6), and supramolecular and macrocycles (Sect. 7).

3 Ground-State Properties

3.1 Conformational Studies

The conformational properties of aromatic heterocycles are related to those of phenyl rings but with the added perturbations due to heteroatoms. We have carried out a systematic study of what we called aromatic propellenes, the heterocyclic analogs of hexaphenylbenzene (**13**) [27, 28], which possess interesting conformational [29] and metal complexing properties (**14**) [30].



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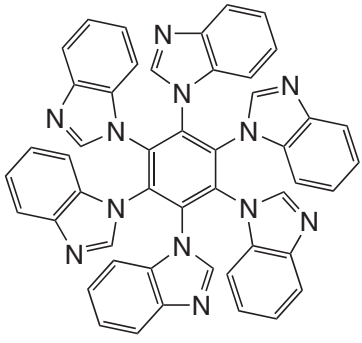

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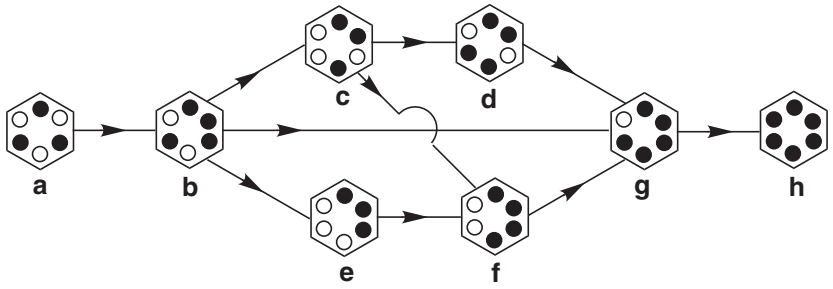
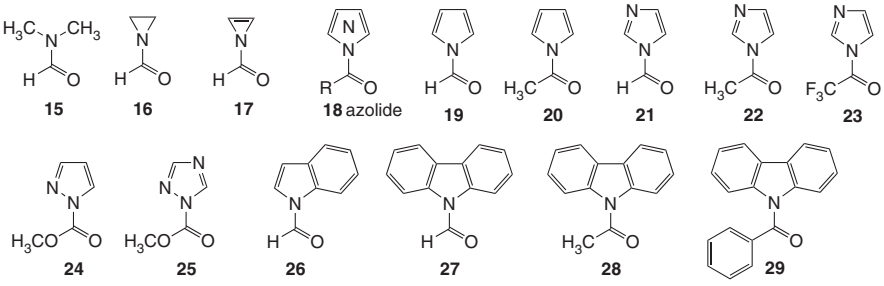


Fig. 1 Interconversion paths between the **a–h** conformers of **14.** *Black circle* denotes that N(3) atom is up, and *white circle* that it is down

Hexakis(benzimidazol-1′-yl)benzene (**14**) [29], due to the loss of symmetry on going from the phenyl to the 1*H*-benzimidazolyl ring, can exist in eight conformations (Fig. 1a–h), depending on whether the N(3) atom is up (black circle) or down (white circle). A mixture of three conformers were isolated and identified (Fig. 1c, e and f).

Another example where aromaticity plays an important role is the barrier to the rotation of amides (compound **18** is represented with N in the middle to indicate any azole) [31]. In classical amides, like dimethylformamide (**15**), the calculated barrier is 80.1–81.0 kJ mol^{-1} (MP2/6-311++G**), which compares well with the experimental barriers of 91.2 (solution) and 85.8 kJ mol^{-1} (gas-phase) [32]. The cases of *N*-formylaziridine (**16**) and *N*-formyl-2-azirine (**17**) are more complex due to the pyramidalization of the nitrogen atom and the presence of rotation and inversion barriers [32]. The effect of the antiaromatic character of 2-azirine (four electrons) [18] on the barrier is difficult to assess due to changes in the ring strain.



When the nitrogen atom of the amide belongs to an azole (aromatic five-membered ring) the lone pair is less available to conjugate with the carbonyl group because it is part of the aromatic sextet [33]. In some way the barrier in azolides (**18**) is an indirect measure of the aromaticity of the azole, or more precisely of the ability of the N1 lone pair to share its electrons. The calculated and experimental values of a series of barriers of azolides are reported in Table 1 [34].

Table 1 Calculated (RHF/6-311G**) and experimental barriers of azolide rotations (in kJ mol^{-1})

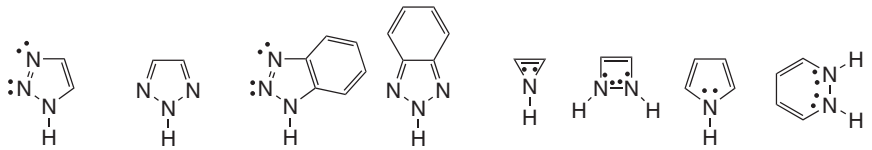
Azolide	Calculated	Experimental	Azolide	Calculated	Experimental
19	55.6	58.6	**20**	53.1	50.6
21	57.3	49.0	**22**	49.4	44.4
23	46.0	42.7	**24**	49.4	43.5
25 (*E*→*Z*)	49.4	45.6	**25** (*Z*→*E*)	44.4	42.3
26	65.3	62.3	**27**	61.9	62.3
28	36.0	39.7			

We have extended these studies to five *N*-benzoylazoles (imidazole, pyrazole, indole, benzimidazole and carbazole) [35] but this time centered on crystallography and solid state NMR. 9-Benzoylcarbazole (**29**) has a low barrier (29.7 kJ mol^{-1}) and shows spontaneous resolution (both axial enantiomers were separated by crystallization). Recently, *N*-benzoylpyrazoles have been described as inhibitors of human neutrophil elastase [36].

3.2 Tautomerism

The relationship between tautomerism and aromaticity is strong both in carbocyclic chemistry (e.g., phenol) [37, 38] and in heterocyclic chemistry (e.g., 2-hydroxypyridine) [39, 40]. We consider that the cycle should be formed by covalent bonds, thus excluding the possibility that rings comprising hydrogen bonds, the so-called resonance assisted hydrogen bonds (RAHB), could be aromatic [41–45].

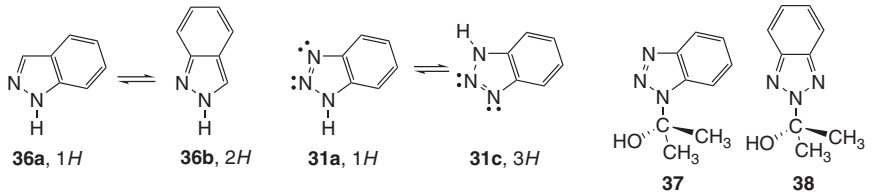
We have devoted three papers explicitly to the relationships between aromaticity and tautomerism; the first to the tautomerism of 1,2,3-triazole (**30**) and benzotriazole (**31**) [46]. If, in the first case, the relative stabilities are determined by the lone-pair/lone-pair repulsion of the adjacent lone pairs that destabilize **30a**, in the second case this is partly compensated by the greater aromaticity of the benzenoid structure **31a**. In the second paper, we discuss the aromaticity of formal 4π-electron antiaromatic 1*H*-2-azirine (**32**), 6π-electron aromatic 1,2*H*-3-diazetine (**33**), pyrrole (**34**), and 1,2-dihydropyridazine (**35**) [47]. Compounds **33** and **35** are not planar and not aromatic.



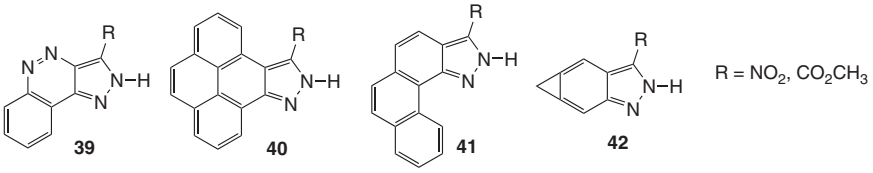
30a, 1H **30b**, 2*H* **31a**, 1*H* **31b**, 2*H* **32** **33** **34** **35**

Finally, the case of indazole (**36**) was theoretically studied and the tautomerism compared to that of **31** [48]. Since now there is no lone-pair/lone-pair

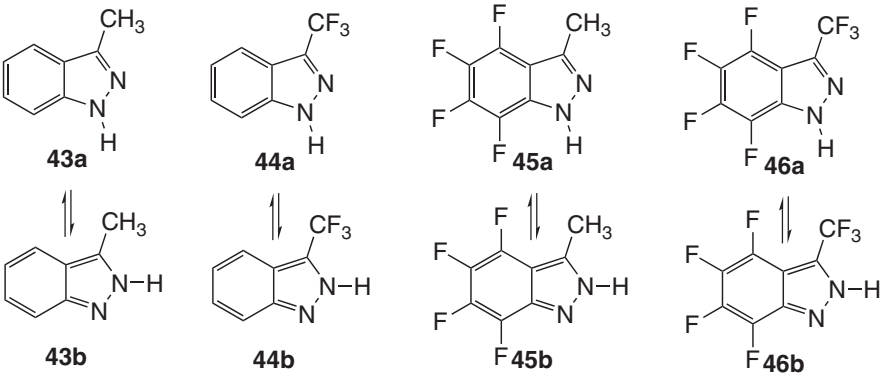
repulsion, the aromaticity of **36a** makes this tautomer much more stable than **36b**.



We have revisited the problem of the tautomerism of benzotriazoles and indazoles [49–51]. Benzotriazole in solution is in a degenerate equilibrium between both aromatic tautomers **31a** and **31c** (the amount of tautomer **31b** is negligible), and the corresponding barrier to proton transfer in acetone-d_6 is 52 kJ mol^{-1} [49]. At low temperature in this solvent, adducts **37** and **38** are formed, the ratio being 4.75 in favor of **37**. We later carried out an extensive theoretical study on the tautomerism of indazole (**36**) and related compounds at the B3LYP/6-31G* levels [50]. We were interested in finding exceptions to the general rule that 1*H*-indazoles are more stable than 2*H*-indazoles. There are several examples **39**–**42** where this inversion in stability is predicted.

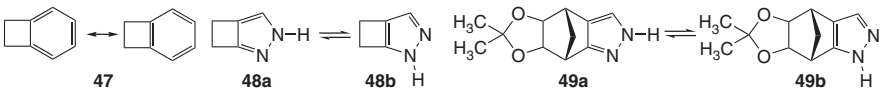


Our last study concerning indazoles was an experimental (X-ray crystallography, NMR spectroscopy in solution and in the solid state) and theoretical study of fluoro-substituted indazoles **43**–**46** [51].



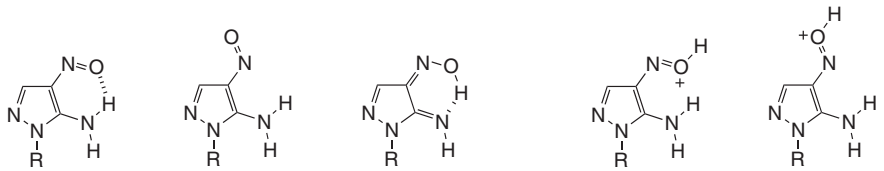
In all cases, the 1*H*-tautomer **a** is the most stable. Both 3-trifluoromethyl derivatives **44** and **46** crystallize in the form of helices of threefold screw axis (chiral group $P3_2$). Hydrogen bonds and aromatic interactions are necessary to rationalize the crystal structures [51].

The Mills–Nixon effect (**42** is a previous example) is a very controversial principle according to which the structures (resonance forms) with an *endo* single bond should be favored [52]. Some authors reject its existence [53–55] while others believe firmly in it [56–61]. We have proposed that there is some parallelism between the resonance forms of the classical Mills–Nixon **47** effect and the tautomeric forms of some heterocyclic compounds **48**.

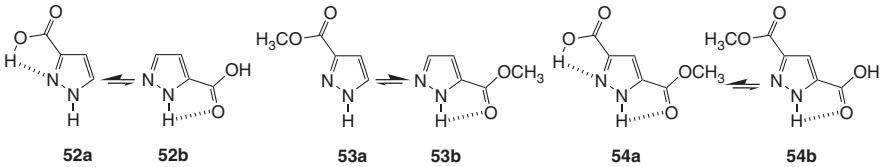


Obviously the annular tautomerism of, for instance pyrazoles, and the resonance forms of 1,2-dihydrocyclobutabenzene are fundamentally different, but one can assume that the experimentally measurable equilibrium constant in **48** will reflect the Mills–Nixon effect [62–65]. Calculations show that the effect should be very considerable with small rings (cyclobutane, **48**, cyclopropane, **42**) that are difficult to synthesize. However, we have succeeded in preparing compound **49** that exists as **49a**, as predicted by the Mills–Nixon effect [65].

The tautomerism of other pyrazoles has also been studied. The examination of the tautomerism, protonation, and *E*/*Z* isomerism of a 4-nitroso-5-aminopyrazole and its salts shows that this compound exists as a mixture of two amino/nitroso isomers **50a** and **50b**; the imino/oxime tautomer **50c** was not present [66]. The salt is a mixture of isomers **51a** and **51b** resulting from the protonation on the oxygen of the nitroso tautomers. The functional tautomerism of 1,5,6,7-tetrahydro-4*H*-indazol-4-ones (a pyrazole derivative) has been studied theoretically and experimentally [67]. In the case of imidazoles 2-substituted by Se, there is experimental evidence that the selenone is more stable than the selenol tautomer [68].

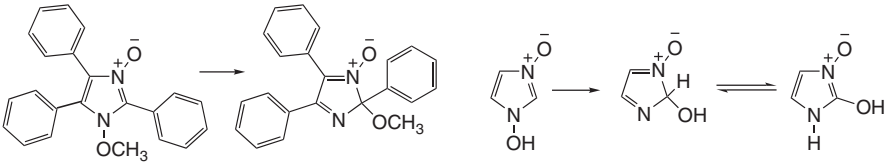


The influence of intramolecular hydrogen bonds on the annular tautomerism of pyrazoles in the case of 3(5)-CO_2H and CO_2Me substituents was rationalized through B3LYP/6-31+G** calculations of 106 tautomers and conformers [69]. It appears that the O–H···N hydrogen bond (**52a**, **53a**) is stronger than the N–H···O one (**52b**, **53b**, **54a**, **54b**).



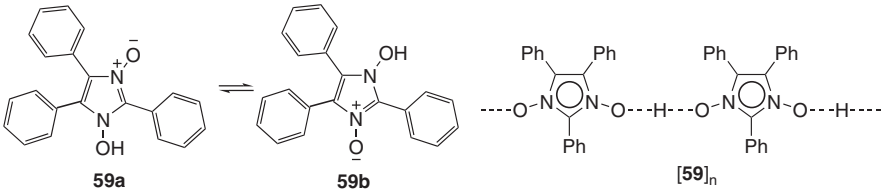
52a **52b** **53a** **53b** **54a** **54b**

In an attempt to prepare the lophine (2,4,5-triphenylimidazole) derivative **55**, we instead obtained **56** [70]. This corresponds to a [1,5]-sigmatropic migration of a methoxy group and proves that the "nonaromatic" structure **56** is more stable than the "aromatic" one **55**. This prompted us to examine theoretically the problem and study the related case of **57**/**58** [71]. At the G3B3 level the relative stabilities of **57**, **58a,** and **58b** (in kJ mol^{-1}) are 202.3, 41.3, and 0.0, respectively. These studies were extended to other substituents (like fluorine) and to other azoles (like pyrazoles).



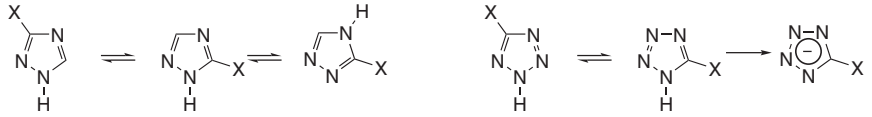
55 **56** **57** **58a** **58b**

The crystal molecular structure of N^1-hydroxylophine N^3-oxide (=1-hydroxy-2,4,5-triphenyl-1*H*-imidazole 3-oxide) (**59**) has been determined [72]. This compound presents a case of degenerate or autotrope tautomerism (**59a** and **59b** are identical), which is very common in annular tautomerism of NH-azoles but very rare in functional tautomerism [40]. In the solid state, the tautomeric proton is in the middle between two consecutive monomers of the catemer $[\mathbf{59}]_n$ [72].



59a **59b** $[\mathbf{59}]_n$

Besides pyrazoles and imidazoles, we have extended these studies to other azoles, for instance to *C*-halogeno 1*H*-1,2,4-triazoles **60** (X = Cl, Br) [73] (for DFT studies of other C-substituted 1,2,4-triazoles, see [74]) and to 5-substituted tetrazoles **61** (X = H, CH_3, *t*-Bu, C_6H_5, Cl, CF_3, NO_2) [75]. The 1,2,4-triazole series **60** was examined regarding tautomerism in solution and in the solid state (the most stable is **60a** and the least stable **60c**). The paper on 5-substituted tetrazoles **61** concerns, besides tautomerism, their ionization (proton loss) to tetrazolate anion **62**.

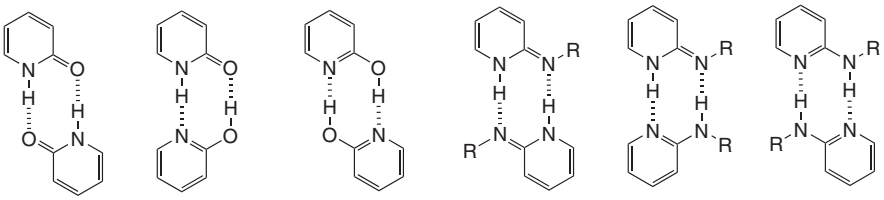


60a **60b** **60c** **61a** **61b** **62**

There is a structural and energetic relationship between the isomerism of azolides (**18**) (acylotropy) and the annular tautomerism of the corresponding NH-azoles [34]. This is due to the lability of the azole–COR bond; for instance, in 1,2,4-triazole the most stable tautomer is the 1*H* (**60a**, X = H) and the only known azolide the 1-COR (related to **25**).

The tautomerism of functional derivatives of azines (e.g., pyridones) and other more complex systems (guanines, porphyrins, etc.) has been much studied both experimental and theoretically [40, 76–82]. Our contribution to this field has been modest: using a combination of ^{13}C and ^{15}N NMR in solution and in the solid state, together with GIAO//B3LYP/6-311++G** calculations, the tautomerism of 2-pyridone, 4(3*H*)-pyrimidone, uracil, and cytosine were determined [83].

The relationships between tautomeric equilibrium constants and intramolecular hydrogen bonds (IMHB) are well documented. As expected, an IMHB stabilizes the tautomer that presents it in comparison with other tautomers without IMHB. On the other hand, information about the effect of intermolecular hydrogen bonds on the thermodynamic aspect of tautomerism is scarce. These HBs are of paramount importance in the solid state; in solution, the situation is more complicated because there are several possible associations that exist in dynamic equilibrium. For this reason we devoted a theoretical paper to this question, studying homo- and heterodimers of 2-pyridone (**63**, **64**, **65**) and 2-aminopyridines (**66**, **67**, **68**) [84]. In the case of pyridone the most stable dimer is **63**; for 2-aminopyridine, it depends on the nature of R.

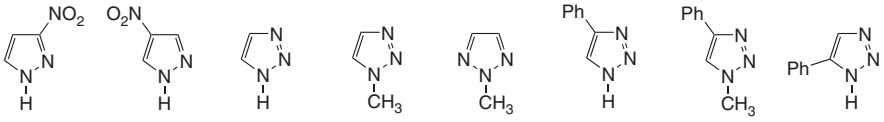


63 **64** **65** **66** **67** **68**

3.3 Acid–Base Equilibrium and Protonation

Many heterocycles, for instance NH-azoles, have acid–base properties of either or both proton gain (basicity) and proton loss (acidity) [85]. The possibility of studying such processes in the gas-phase (mass spectrometry and Fourier transform ion cyclotron resonance – FTICR – spectroscopy) provides theoreticians with values

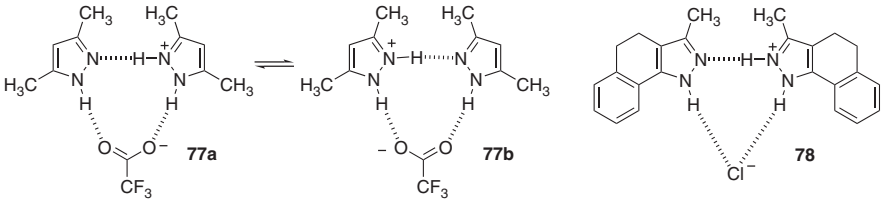
clean of solvent effects. In this way we determined that 3-nitropyrazole (**69**) and 4-nitropyrazole (**70**) in the gas phase at equilibrium protonate on the heterocyclic N2 nitrogen rather than on the oxygen of the nitro group [86].



69 **70** **71** **72** **73** **74** **75** **76**

The gas-phase and aqueous basicities of six 1,2,3-triazoles (**71**–**76**), have been determined, the former by FTICR and the latter by spectrophotometry and ^{1}H NMR. The gas-phase experiments are in good agreement with the Gibbs free energies calculated at the B3LYP/6-31G* level. In contrast, only semiquantitative ascertainments are possible when basicities in the gas phase and in solution are compared. The equilibria involved are complex due to tautomerism [87].

The acid–base properties of 4-nitroso-5-aminopyrazoles **50** have been studied. In particular, protonation sites have been determined where salts **51** are formed [66]. The effects produced on ^{1}H, ^{13}C, and ^{15}N chemical shifts by protonation and by hydrogen-bonding solvents on five azoles (imidazole, 4,5-dimethylimidazole, pyrazole, 3,5-dimethyl-pyrazole, and 4,5-dihydro-3-methyl-2*H*-benz[*g*]indazole) have been determined experimentally. Phase effects on the ^{13}C chemical shifts of the C-4 atom of pyrazole were discussed, based both on empirical models and on GIAO calculations of absolute shieldings in different complexes. The special case of the chemical shifts of pyrazoles in the solid state, where they form multiple N–H···N hydrogen bonds, was also studied theoretically [88].



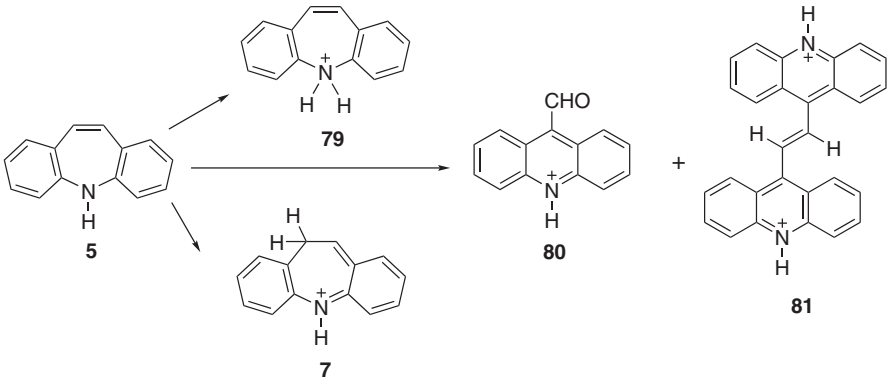
77a **77b** **78**

The main conclusions were:

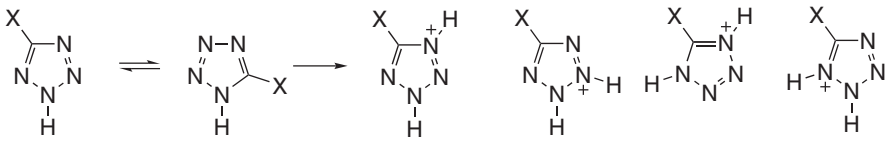
1. For the molecules or complexes reported in this study, the absolute shieldings calculated at the GIAO/B3LYP/6-311++G** level provide a correct picture of the most important effects, such as protonation, deprotonation, formation of hemi-salts, etc.
2. Solvent effects on ^{13}C NMR signals are too feeble to be properly described by supermolecules although complexes containing two water molecules represent fairly well the situation in solvents like methanol.
3. The dynamic situation of the hemi-trifluoroacetate of 3,5-dimethylpyrazole (**77**) has been clarified.

4. By a combination of NMR data in the solid state and GIAO calculations, the existence of a proton transfer in hemi-salt **78** (solid state proton transfer, SSPT) has been established. This is an important result because SSPT remains an infrequent phenomenon (see Sect. 3.4).

To explore the possible antiaromaticity of 5*H*-dibenz[*b*,*f*]azepine (**5**) we have studied its behavior in sulfuric acid as a solvent using NMR (including GIAO calculations) [89]. Instead of the expected cations **79** and **7** we isolated the cations of 9-formylacridine (**80**) and of 9,9¢-ethene-1,2-diyl-bis-acridine (**81**). A mechanism for this unexpected dismutation was proposed.

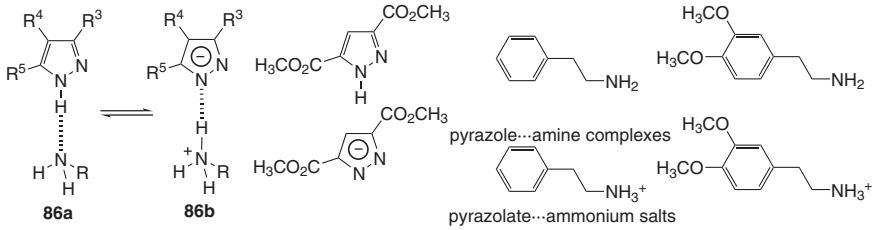


We have already discussed the acidity of NH-tetrazoles **61** to form tetrazolate anions **62** [75]. In the same paper, we also studied the protonation. The substituent X strongly affects the tautomeric balance between 1,3-H,H$^+$- (**82**) and 1,4-H,H$^+$-cations (**84**). In the case of electron-withdrawing substituents, the most preferred form of the conjugated acid is the 1,3-H,H$^+$- form (**82**); structures **83** and **85** are much less stable. The acidity measures in solution and in the gas phase satisfactorily correlate with each other. In all cases, these relationships do not hold for 5-phenyltetrazole (**56**, X = Ph) . This could be explained by the difference in solvation of this compound compared to other 5-X tetrazoles as well as by some peculiarity of its electronic structure, for example, the strong conjugation between the phenyl substituent and the tetrazole ring.



There is a very common and difficult problem concerning the structure of protic salts in the solid state when X-ray resolution is not enough to unambiguously locate

the protons. For instance, is the nature of the solid that precipitates in some cases when mixing pyrazoles and amines (the actual compounds studied are shown on the right side) a pyrazole·amine complex **86a** or a pyrazolate·ammonium salt **86b**? Note that these structures are prototropic tautomers. Using ^{13}C and ^{15}N solid-state NMR combined with GIAO calculations, we have determined that the structure is **86b** [90].

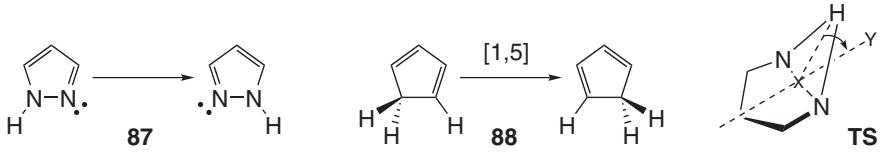


3.4 Proton Transfer

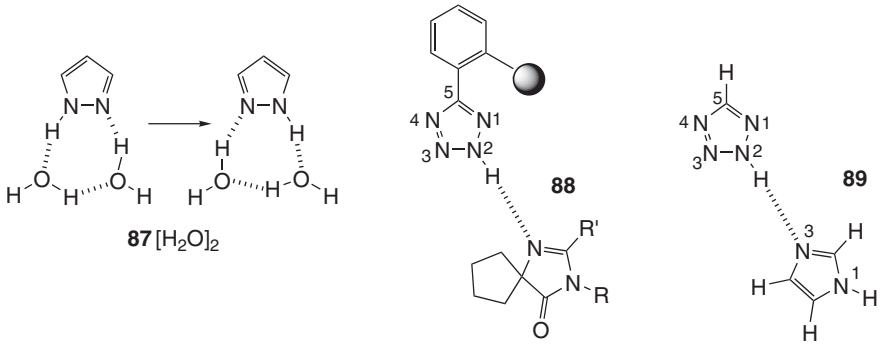
Proton transfer (PT), i.e., the kinetic aspects of heteroaromatic prototropic tautomerism, is an important and somewhat neglected topic or, at least, much less studied than the thermodynamic aspects (equilibrium constants, acidity, basicity, pK_a, etc.). Intermolecular proton transfer between two heterocycles, one protonated and one neutral, occurs along a hydrogen bond (see Sect. 3.5). When the proton transfer occurs in a crystal or in an amorphous solid, we speak of SSPT (vide supra).

Consider for instance, 1*H*-pyrazole (**87**). It is known that proton transfer between both nitrogen atoms (leading to tautomerism) occurs in the gas phase, in solution and, in some cases, in the solid state (depending on the substituents on the carbon atoms). Is the process an intramolecular 1,2-shift? Theoretical calculations show that this is a very high-energy process, almost forbidden [91] (214 kJ mol^{-1} at the B3LYP/6-31G* level). Then, the logical conclusion is that proton transfer in azoles involves solvent molecules (solution) or other azole molecules (solid state).

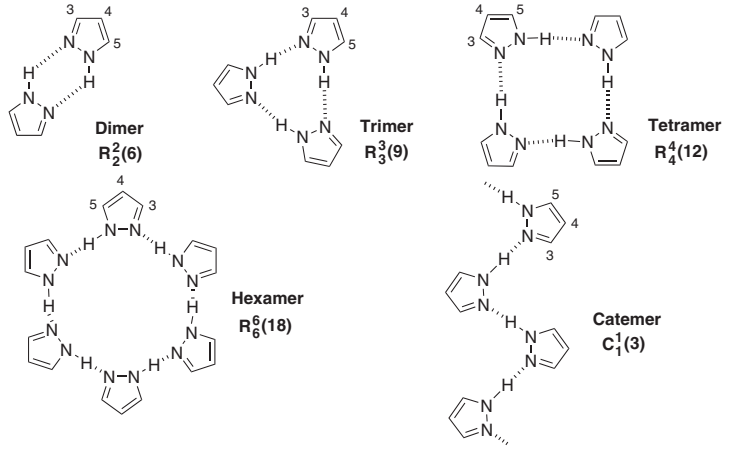
We have studied the intramolecular PT in **87** and compared it with the [1,5]-sigmatropic rearrangement of cyclopentadiene (**83**) [91], noting the profound differences between these two systems. In pyrazole, the N(sp^2)–N(sp^2) bond is essential while in cyclopentadiene the C(sp^3)–C(sp^2) bond is accessory. The **TS** in pyrazole corresponds to a structure with the proton equidistant from both N atoms and clearly out-of-plane (HXY = 63.4°). Intramolecular PT in antiaromatic 2-diazirine and 1,2-diazepine were studied as counterexamples.



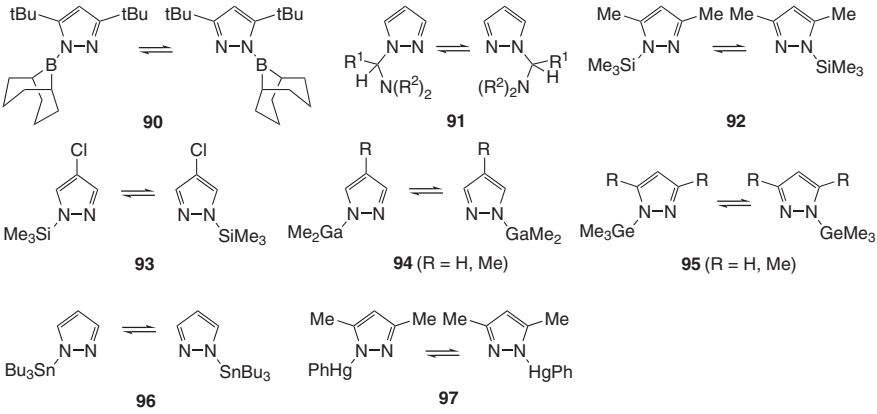
We then studied PT in pyrazole **87** assisted by solvent molecules, noting that two water molecules decrease the barrier to 2 kJ mol^{-1} [92]. In the same publication, we modeled the case of Irbesartan (a powerful angiotensin II antagonist used for the treatment of hypertension) [93]. This compound crystallizes in the solid state, forming dimers linked by N–H···N HBs **88** that present SSPT between tetrazole N2 and N3 nitrogen atoms. We have simplified **88** into structure **89**, a 2*H*-tetrazole hydrogen-bonded to the N3 of imidazole. In the absence of imidazole, the PT barrier amounts to 210 kJ mol^{-1} (B3LYP/6-311++G**) while in the presence of imidazole the barrier is lowered to 119 kJ mol^{-1}. The barrier is further lowered if the crystal structure is simulated with a solvent cavity of the Onsager type ($\varepsilon = 5$) to 67 kJ mol^{-1} [92]. These studies are relevant for proton conduction in polymer electrolyte membranes by 2*H*-1,2,3-triazole (**30b**) [94].



According to Stride: "the cyclic pyrazoles are an intriguing family of relatively simple organic molecules displaying a complex interaction of attractive dipolar hydrogen bonding and repulsive intermolecular interactions, leading to a range of structural motifs and unusual physical properties" [95]. Etter/Bernstein graph set descriptors are given for each motif [96–99] as shown below.



We studied, at the B3LYP/6-31+G** theoretical level, four monomers and 12 NH–pyrazole cyclamers, C-unsubstituted or bearing fluoro, chloro and bromo substituents at positions 3 and 5 [100]. Two mechanisms of proton transfer, stepwise and synchronous, were calculated for dimers, trimers, and tetramers. The set of values of energies and geometries thus obtained provide useful insights about the dynamics of NH–pyrazoles in the solid state. It has been shown that pyrazole cyclamers exist not only in condensed phases but in the gas phase as well [101], thus our "gas-phase" calculations will provide information about the solid state.



There is abundant literature on N-to-N migration of groups different from the proton [102]. With due simplifications, the transition states corresponding to **90**–**97** were calculated theoretically at different levels (B3LYP and MP2 with 6-31G*, 6-311G*, and CEP-121 basis sets). The ten groups studied were H, BH_2, CH_3, CHO, AlH_2, SiH_3, GaH_2, GeH_3, SnH_3, and HgH. Two types of different transition states were found, the most common being a triangular situation with the group symmetrically linked to both N atoms. For metals of group 13 (M = B, Ga, Al), that situation is a second minimum while the TS corresponds to a rotation about the N–M bond, plus a displacement of the migrating group to yield a non-symmetric TS.

Two other papers relevant to proton transfer are one on pyrazole-4-carboxylic acid [103] and another on proton transport along molecular wires [104]. Using high-resolution solid-state ^{15}N CPMAS NMR, X-ray crystallography, and ab initio calculations, we have studied the structure of solid pyrazole-4-carboxylic acid (**98**). The crystal structure was determined at 295 and 150 K (see Fig. 2). Molecules of **98** are located on a twofold axis, implying proton disorder of the NH and OH groups; no phase transition was observed between these two temperatures. The compound forms quasi-linear ribbons in which the molecules are linked by cyclic hydrogen bonds between pyrazole and carboxylic acid groups, with disordered hydrogen-bonded protons.

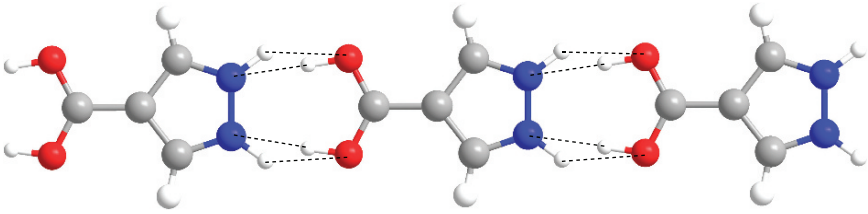
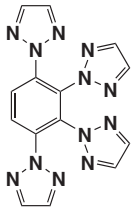


Fig. 2 X-ray molecular structure of pyrazole-4-carboxylic acid (**98**)

Crystallography is unable to decide whether the disorder is dynamic or static. NMR shows that this disorder is dynamic, that is, consisting of very fast degenerate double proton transfers between two rapidly interconverting O–H···N and O···H–N hydrogen bridges. However, at low temperature, NMR shows a proton disorder–order transition where the protons are preferentially localized on given nitrogen and oxygen atoms. An amorphous phase exhibiting proton order is observed when the compound is precipitated rapidly. In this case, the defects are annealed by moderate heating. Ab initio calculations performed on oligomers of **98** show that the O–H···N hydrogen bridge is about 0.064 Å shorter and less bent (171°) than the O···H–N hydrogen bridge (150°). For an isolated ribbon, this result leads to structures with localized protons: to a cycle with about 200 molecules, to a quasi-linear ribbon involving an undulated structure, or to a combination of both motifs. Only the undulated structure is compatible with the linear ribbon observed by X-ray crystallography, where the fast proton transfer in the high-temperature phase is assisted by the motions of the undulated chain. A disordered structure is assigned to the amorphous phase, which exhibits the combination of curved and undulated motifs.

To conclude this section on proton transfer, we have examined an alternative mechanism to that of von Grotthuss for proton conduction [105–110]. We carried out B3LYP/6-31+G** and PW91 DFT calculations on model compounds (1,2,3,4-tetrasubstituted benzenes, e.g., **99**) showing that these compounds could play the role of proton conductors [104].



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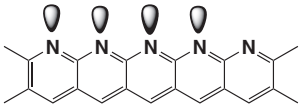
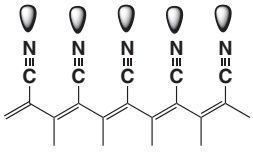
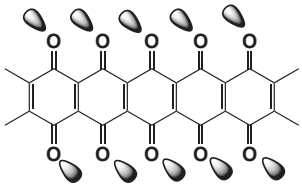
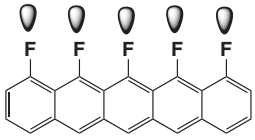


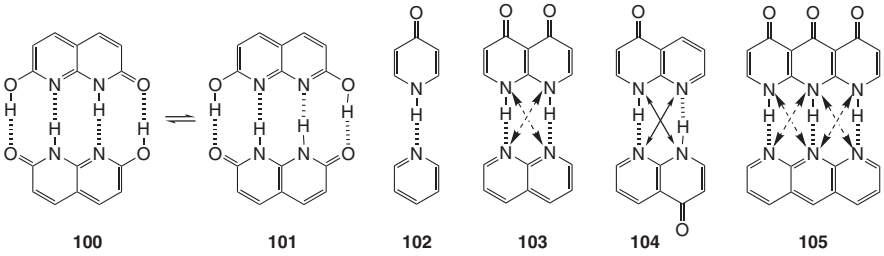






3.5 Hydrogen Bonds

Besides the aspects already discussed in previous sections (Sects. 3.2, 3.3, and 3.4) we would like to discuss the subject of secondary interactions introduced by Jorgensen [111, 112] for dimers linked by multiple hydrogen bonds (MHBs, shown below). The existence of MHBs is essential for replication and recognition in both DNA and RNA. From the third HB onwards, the stabilization is no longer additive. The behavior of three 2,7-disubstituted 1,8-naphthyridines able to exhibit tautomerism was studied by NMR in solution and in two cases in the solid state. The three derivatives studied were 2,7-dihydroxy-, 2-acetamido-7-amino-, and 2,7-diacetamido-1,8-naphthyridine. For instance, 2,7-dihydroxy-1,8-naphthyridine dimers can exist as homodimers **100** (two degenerate tautomers) and as heterodimers **101**. To explore the problem of secondary interactions, we studied a series of complexes, **102**–**105**, with up to four simultaneous hydrogen bonds, where the monomers are generated using pyridine and 4-pyridone as building blocks [113].



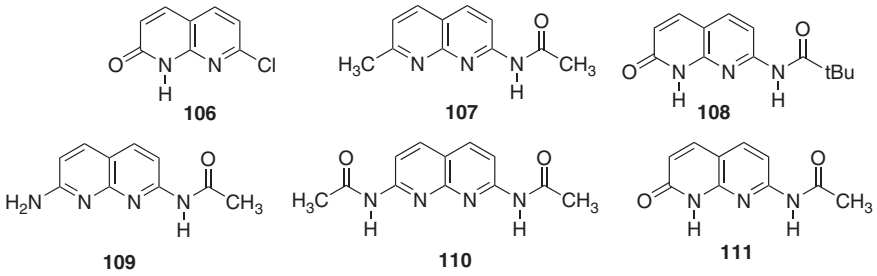
100 **101** **102** **103** **104** **105**

The analysis of these non-pairwise effects allowed us to estimate that the repulsive secondary interactions are twice as large as the attractive ones (+9 vs. −4 kJ mol^{-1}). This model has been used to rationalize the case of 2-oxo-7-hydroxy-1,3-dihydro-1*H*-1,8-naphthyridine, a compound existing in the solid state probably as the **101** dimer with four intermolecular HBs and having the possibility to sustain SSPT. Unfortunately, the amide derivatives do not exist as amino/imino tautomers but as the diamino (diacylamino) tautomers and, therefore, cannot present the four HBs necessary for SSPT. We have extended these studies to other difunctional naphthyridines [114].

Combination of two hydrogen-bonding units in preorganized scaffolds is an effective way to achieve a dimer or a supramolecular polymer (Fig. 3).

We have used 2,7-disubstituted naphthyridines with hydroxy and amido groups to achieve a variety of molecular structures including M and P helices. A combination of X-ray crystallography and theoretical calculations on model compounds (B3LYP/6-31+G**) was used to discuss the tautomerism and the hydrogen bonds of compounds **106**–**111** [114]. Compound **111** was used in the calculations instead of **108**.

Fig. 3 Self-association of individual molecules can lead to the formation of complex aggregates



Note than in most X-ray structures of aromatic NH-heterocycles, the N–H···N hydrogen bonds are of fundamental importance (Sect. 3.7).

3.6 Calorimetry and Thermodynamics

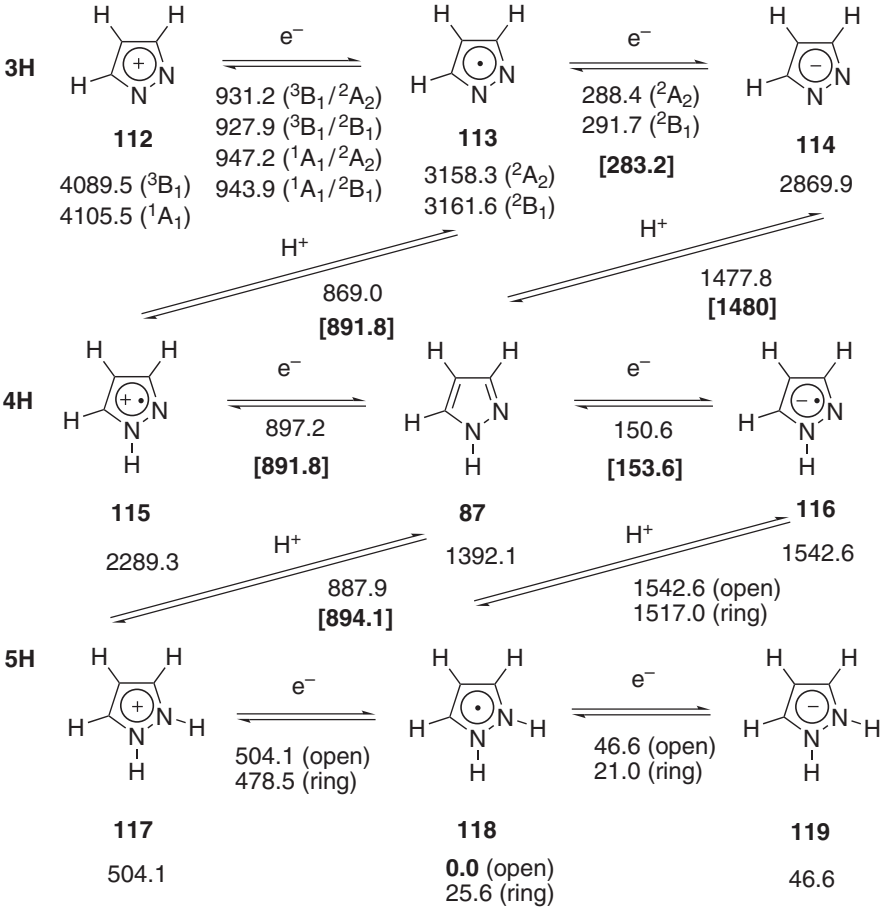
Although the importance of calorimetry for the characterization of aromatic heterocycles is considerable, our contribution has been scarce. We have already reported the case of compounds **60** and **61** [71]. While B3LYP/6-31G* and G3B3 (G3//B3LYP) calculations affirm that the aromatic 1*H*-imidazole and 1*H*-pyrazole are more stable than their nonaromatic tautomers, this stability is reversed when the hydrogen on the azole nitrogen or methylene carbon is replaced by OH or by F, for example. In increasing order of stability we find 1-fluoro-1*H*-imidazole <2-fluoro-2*H*-imidazole (<2-fluoro-1*H*-imidazole). These results are related to a recent report of a highly substituted imidazole that exists in the "nonaromatic" 2*H*-tautomeric form, a result also discussed in a purely thermochemical context [115].

We have carried out a systematic study of pyrazole derivatives (neutral, anions, cations, radicals) at the G3B3 level of the ten equilibria present in the below structure [116]. The values under each structure are the energies in kJ mol^{-1} with regard to the absolute minimum, compound **118**. The numbers close to the double arrows correspond to the equilibria and are the differences between the former values.
The main conclusions of this study are:

1. There are ten equilibria between species, from which six have been measured experimentally and the agreement is excellent
2. Two structures, cyclic and chain, have been found for the pyrazolio-radical **118** that are able to explain the electrochemistry of pyrazolium salts
3. The aromaticity, calculated as the NICS indexes, are related to the unexpected stability of the pyrazole anion **114**.

3.7 Crystallography

The molecular structure of heterocycles as determined by X-ray crystallography is an important source of information related to aromaticity [117]. In the case of NH-pyrazoles, our main subject, we have published two papers [118, 119] concerning the classification of hydrogen-bonded motives in these compounds. The first approach was empirical and extrathermodynamic but the second one, a search in the Cambridge Structural Database [120, 121] for NH-pyrazoles lacking other hydrogen-bond donor and acceptor sites, identified 49 compounds that crystallize in 47 structures forming dimers (16), tetramers (13), trimers (8), hexamers (1), and catemers (10) using N–H···N hydrogen bonds. These structures were classified into two classes (dimers and tetramers vs. trimers and catemers) using the accessible surface to an atom (sum-F) with good results (Fig. 4). The method was extended to new pyrazoles by means of theoretical calculations (B3LYP/6-31G*) of the geometry



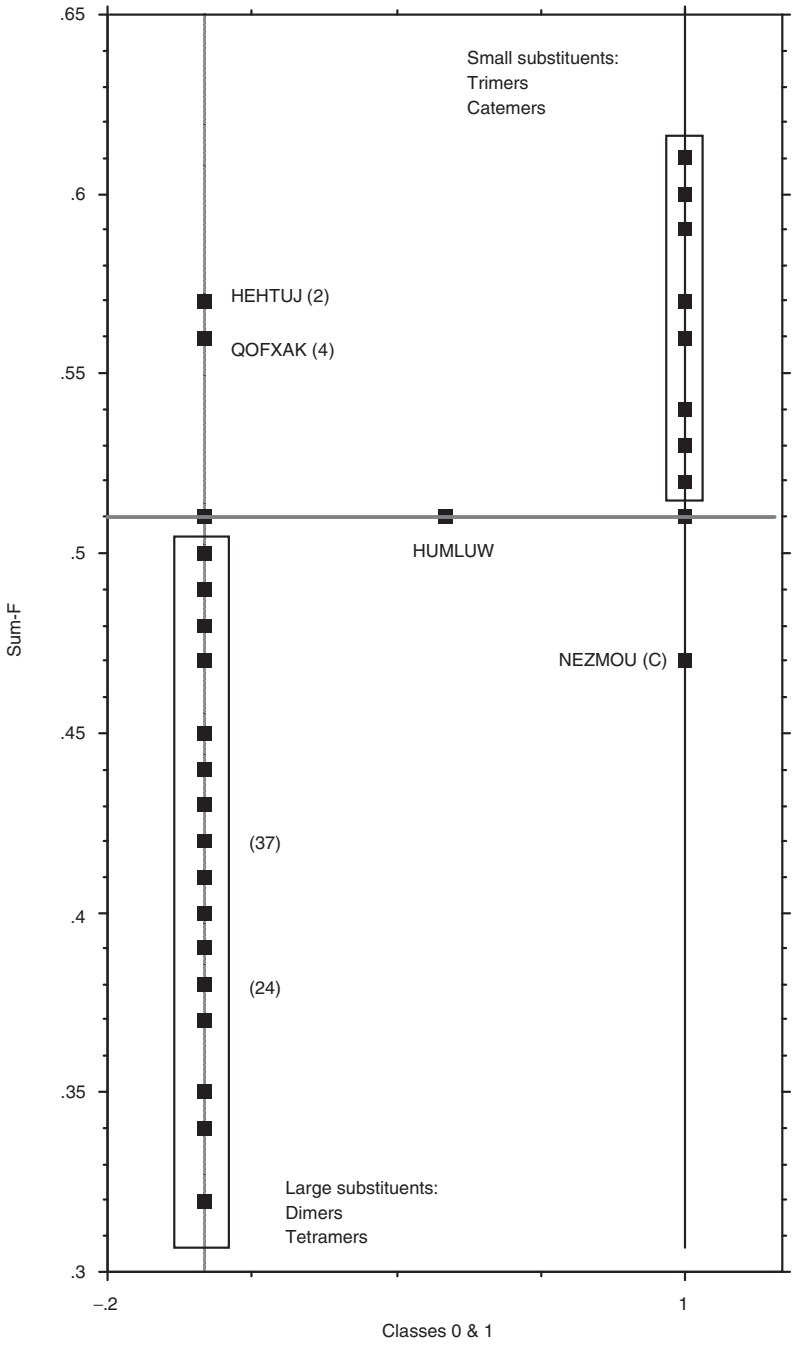
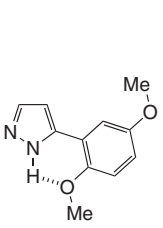


Fig. 4 Representation of the discrimination of NH-pyrazoles using sum-F (2dimer, *4* tetramer, *C* catemer). *Sum-F* corresponds to the accessible surface of the N atom [119]

of the monomers. Aspects such as the conformation of phenyl groups, the additivity of C-substituent effects, and the buttressing effect (presence of 3,4, 4,5, or 3,4,5 substituents) were also studied theoretically. In general, although most calculations correspond to the isolated molecules (i.e., the gas phase), the agreement with experimental geometries is very good for what concerns bond distances and bond angles and less good for what concerns dihedral angles [122]. This is simply related to the different energies involved in the distortion, for instance, C–C 0.1 Å 15 kJ mol^{-1}; C–C–C 10° 4 kJ mol^{-1}; ethane twist 10° < 1 kJ mol^{-1}.

The information from crystallography is enormous so we have selected four issues from the literature according to their greater interest. Halcrow et al. [123] reported that pyrazole **120** exists as 5-Ar tautomer with an IMHB, while the hemihydrate of pyrazole **121** exists as a mixture of both tautomers **121a** and **121b**.



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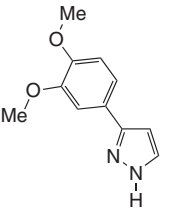
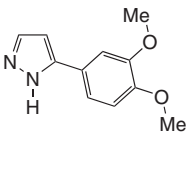
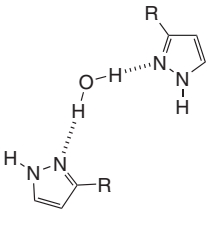


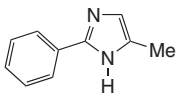
121a



121b



[121a+121b]H_2O



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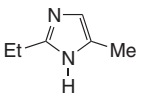

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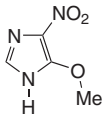
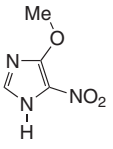
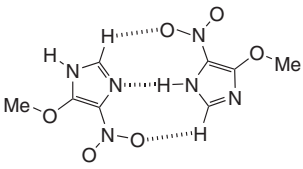


124a



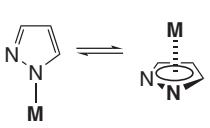
124b



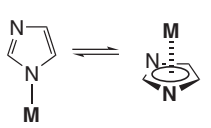
[124a+124b]

Toda et al. reported that inclusion compounds correspond to a unique tautomer, for instance, in the case of imidazoles to 5-methyl tautomers, **122** and **123** [124]. Kubicki described one of the rare cases of both tautomers, **124a** and **124b**, existing together in the unit cell [125]. Remember that the fluoroindazoles of structure (**44**–**46**) present interesting hydrogen-bonded structures including chiral catemers (space group $P3_2$); they are the first examples of indazoles crystallizing in the form of helices with a threefold screw axis [51].

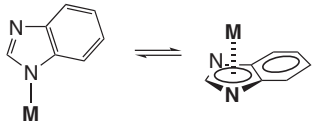
Although most cases of tautomerism concern the proton (prototropy or prototropic tautomerism) other elements can also migrate, including metals (metallotropy). Mexican authors have discussed the structure of pyrazolates of Li^+, Na^+, and K^+ (**125**). The X-ray structures correspond to mixtures of **125a** and **125b** (π-facial tautomer) [126, 127]. Their theoretical calculations show that **125a** is more stable than **125b**.



125a **125b**



126a **126b**

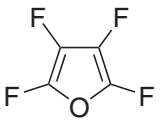


127a **127b**

We have carried out a theoretical study on the related cases of imidazoles (**126**) and benzimidazoles (**127**) [128].

3.8 Heterocycles as π-Acceptors

One of us has used molecular polarization potentials (MPP) to study the interaction of aromatic molecules, including furan, thiophene, and pyridine with a positive unitary charge, these maps being powerful tools for the study of intermolecular interactions and chemical reactivity [129, 130]. This kind of study leads us to examine theoretically the problem of the interaction between cations and anions with aromatic rings. We were pioneers in proposing that, in parallel with cation·π-systems (for instance, benzene), there should exists anion·perfluorinated·π-systems (for instance, hexafluorobenzene) [131]. These studies include tetrafluorofuran and tetrafluorothiophene (**128**, **129**). Simultaneously, Mascal et al. [132] described the same phenomenon but with 1,3,5-triazine (**130**) and 2,4,6-trifluoro-1,3,5-triazine (**131**) as acid π-systems. The group of the University of Palma de Mallorca has published a large number of papers on this topic [133] that are well summarized in a two recent reviews [134, 135].



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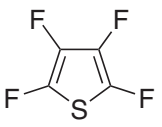

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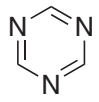

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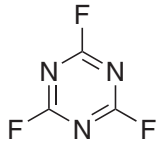


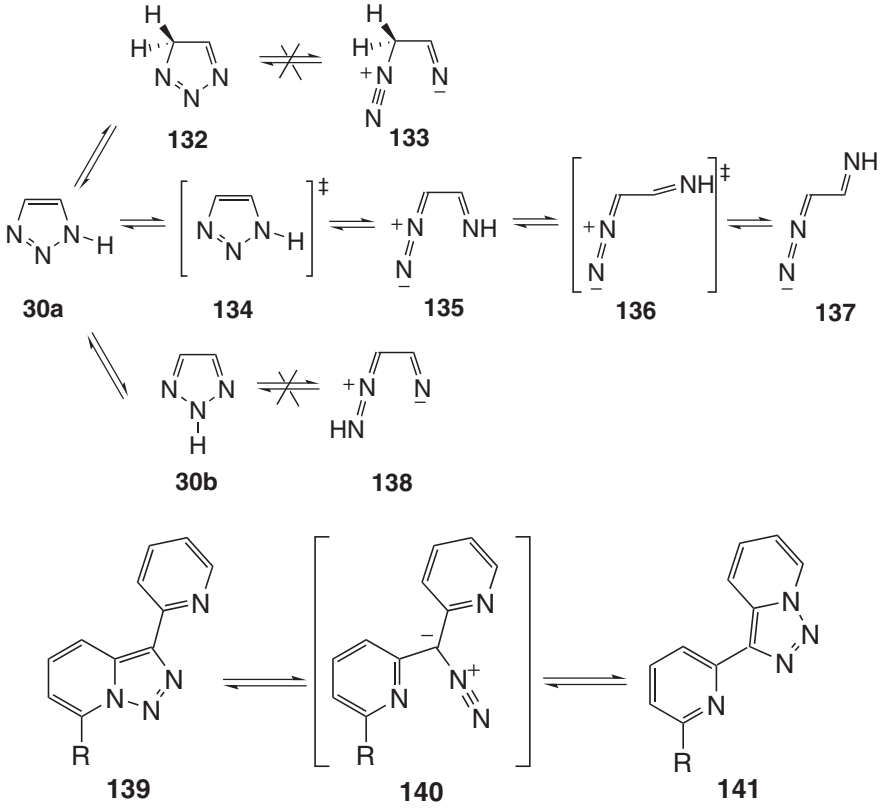
131

4 Reactivity

Our contribution to the reactivity of aromatic heterocycles involves only two papers [136]. In the first one, we carried out IRC calculations (HF/6-31G**) to confirm the connecting structures of each transition state for the 1,2,3-triazole/iminodiazomethane isomerizations. For the triazolate anion, both tautomers of 1,2,3-triazole and several 1,2,3-triazolium cations were studied. The below structure reports the case of the neutral molecules **30a** and **30b**.

The ring–chain process described in the above structure is complementary to the ring opening of 1,2,3-triazoles to vinyl azides that proceeds via intermediate 4*H*-1,2,3-triazoles **132** [137, 138].

Related to the mechanism of the above structure is the ring–chain–ring isomerization of 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyrid-7-yl derivatives (**139**) into 6-{[1,2,3]triazolo[1,5-*a*]pyrid-3-yl}-2-pyridyl derivatives (**141**) via a diazo compound **140** [139].



5 Spectroscopy

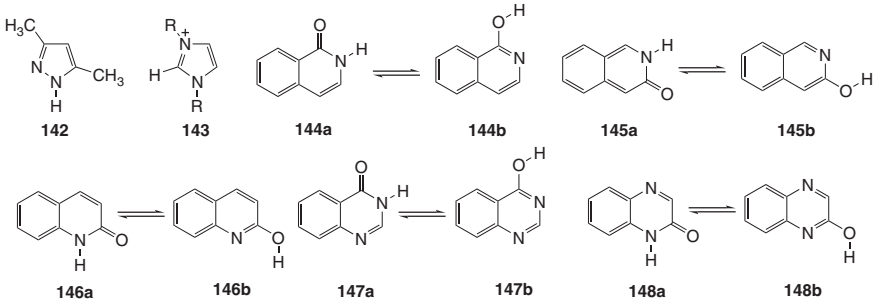
5.1 IR

The results obtained by infrared/Raman spectroscopy can be adequately reproduced by theoretical calculations (frequently a scaling factor must be applied [140]). The infrared and Raman spectra of 3,5-dimethylpyrazole C_5H_7N–NH (**142**) was recorded in the vapor, liquid (melt and solution), and solid states [141, 142]. Two deuterated derivatives, C_5H_7N–ND and C_5D_7N–NH, were also studied in solid state and in solution. The solids are made out of cyclic hydrogen-bonded trimers. These trimers, present also in chloroform and acetone solutions, give rise to characteristic high absorption infrared spectra in the 3200–2500 cm^{-1} region, related to Fermi resonance involving down-shifted *v*(NH) vibrations. Water solutions do not present trimers but show spectral features similar in several ways to those of the trimer, attributable to solvent-bonded complexes. To interpret the experimental data, ab initio computations of the harmonic vibrational frequencies and infrared and

Raman intensities were carried out at the RHF/6-31G* level for the three monomeric compounds as well as for three models of the trimer, with *C3h* , *C3*, and *C1* symmetry. The combined use of experiments and computations allows a precise assignment of most of the observed bands for all the systems. In general, the agreement between theory and experiment is very good, with the exception of the infrared and Raman intensities of some transitions. Particularly noticeable is the failure of the theoretical calculations to account for the high intensity of the Raman bands of the solid at about 115 and 82 cm^{-1}. Amongst the vibrational properties of the trimer are the breathing and deformation bands at 115 and 82 cm^{-1}. The contraction of the trimer during the breathing vibration is the beginning of the process (involving much higher vibrationally excited states) that leads to the transition state of symmetry D_{3h}.

The important field of ionic liquids, in most cases 1,3-dimidazolium salts (**143**) has been studied by IR and Raman spectroscopies supported by B3LYP calculations. Additionally, calculations of the heteroaromaticity (HOMA index) showed that cation formation causes a decrease of the aromaticity of the imidazole ring. However, when the R groups at positions 1,3 are benzyl or adamantyl, the aromatic nature of the heterocyclic moiety increases. Moreover, the electron distribution performed using the GAPT method indicated the positive charge delocalization in the imidazolium ring [143].

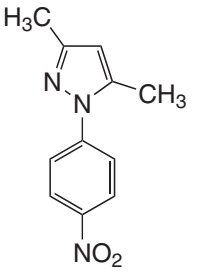
Leszczynski et al. have shown interest in comparing experimental (matrix isolation) and calculated (B3LYP) IR data (frequency and intensity) to discuss the tautomerism of benzo-annelated pyridonone, pyrazinone, and pyrimidinone (**144**–**148**). These equilibria were well reproduced by theoretical calculations carried out at the QCISD and QCISD(T) levels. The combined experimental and theoretical results reveal links between aromaticity and tautomerism. Moreover, a UV-induced phototautomeric reaction transforming the oxo forms into the hydroxy tautomers was observed for all (except 3-hydroxyisoquinoline) studied compounds [144]. The interest of Leszczynski in problems related to tautomerism, aromaticity, and proton transfer is also apparent in a study of (1*H*-azahetero-2-ylidene)-acetaldehyde and 2-azahetero-2-yl-ethanol tautomeric pairs [145].



5.2 NMR δ

One of us has published a review entitled "The use of NMR spectroscopy to study tautomerism" (256 references) where useful information on this topic can be found [146]. Our main contribution to the use of chemical shifts in heteroaromatic compounds has been the systematic calculation of absolute shieldings (σ, ppm) to assign some signals (for instance those that decoalesce on cooling) and to discuss the structure of these compounds. We published another review entitled "GIAO calculations of chemical shifts in heterocyclic compounds" (115 references) [147]. In this review, the GIAO calculations of absolute shieldings and their relationship with experimental chemical shifts for aromatic heterocycles were summarized. Automatic assignment, conformational analysis, *E*/*Z* isomerism, and, in particular, tautomerism were discussed in detail. Solid-state and solvent effects were examined, as well as the problem of heteroaromaticity. The review ends with the discussion of some methodological problems with special emphasis on the calculation of references, such as TMS and nitromethane.

After a paper devoted to GIAO/B3LYP calculations of 13 monosubstituted benzenes and 21 1-substituted pyrazoles [148] that allowed discussion of some structural problems (such as conformation, tautomerism, and structure of salts) we have continued to use this combination of experimental (in solution and in the solid state, CPMAS NMR) and calculated values as a very useful exploratory technique. For instance, we have used ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy to study compounds **149**–**154**. In *para*-disubstituted derivatives **149**, **151**, **152**, **153**, in the solid state (no free rotation) the signals of the *ortho* carbons are split (one is close to N2) and, thanks to the calculated values, they can be assigned [149].



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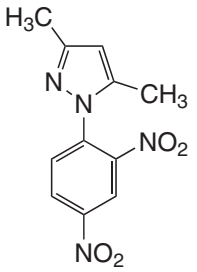

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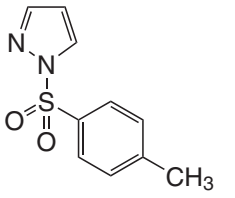

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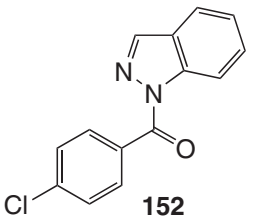

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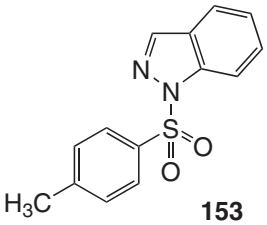

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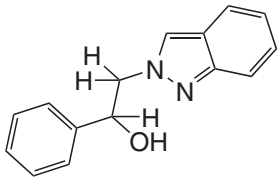
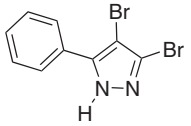


154

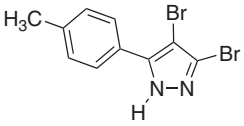
Having compared chemical shifts (δ) and absolute shieldings (σ) many times in these and other studies we decided to put all the data together, add some more compounds to have a regular distribution of the points, and calculate the regression equations with all of them [150]. We did not use data from ^{1}H NMR as it is too sensitive to solvent effects, but only from ^{13}C and ^{15}N NMR studies, using all kinds of data (different solvents and solid-state), general values being preferred even if the precision was lower.

$$\delta^{13}C = (175.7\pm0.2) - (0.963\pm0.003)\ \sigma^{13}C,\ n = 461,\ r^2 = 0.996,\ RMS = 2.9\ ppm$$
$$\delta^{15}N = -(152.0\pm1.1) - (0.946\pm0.008)\ \sigma^{15}N,\ n = 70,\ r^2 = 0.995,\ RMS = 9.1\ ppm$$
$$\delta^{16}N = -(154.0\pm1.9) - (0.874\pm0.010)\ \sigma^{15}N,\ n = 72,\ r^2 = 0.992,\ RMS = 16.0\ ppm$$

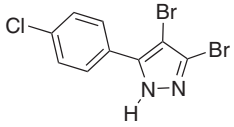
The second equation for ^{15}N includes nitroso derivatives (very far removed from other ^{15}N chemical shifts). The usefulness of ^{15}N chemical shifts (combined with GIAO calculations and some X-ray structure determinations) was demonstrated in the case of *C*-bromo pyrazoles **152**–**158** [151].



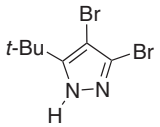
155a



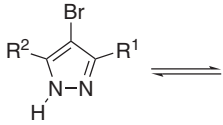
156a



157a



158a



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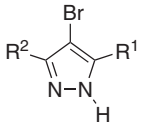

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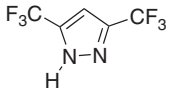


159

In all cases when there is a bromine atom at position 3(5), **155**–**158**, the tautomer present in the solid state is the 3-bromo one **a**. In solution, the same tautomer is the major one. DFT calculations justify the predominance of 3-bromo tautomers over 5-bromo ones and provide some useful chemical shifts obtained through GIAO calculations.

The X-ray molecular structure of 3,5-bis(trifluoromethyl)pyrazole (**159**) was determined at 120 K and gave crystals belonging to the triclinic *P*-1 space group. The compound forms tetramers through N–H···N hydrogen bonds, some proton disorder being necessary to explain the geometric features of the monomers. The IR spectra have been recorded in the gas phase (monomers) and in the solid state (tetramers) and analyzed by comparison with the calculated normal frequencies (see Sect. 5.1). The use of solid-state NMR spectroscopy combined with ab initio GIAO calculations suggests that a certain amount (about 40 ± 10%) of dynamic disorder involving intramolecular proton transfers could be present in the crystal of **159** [152].

There are some situations where the assignment of NMR signals is a very difficult task in the absence of calculated chemical shifts. For instance, in the Mo complex

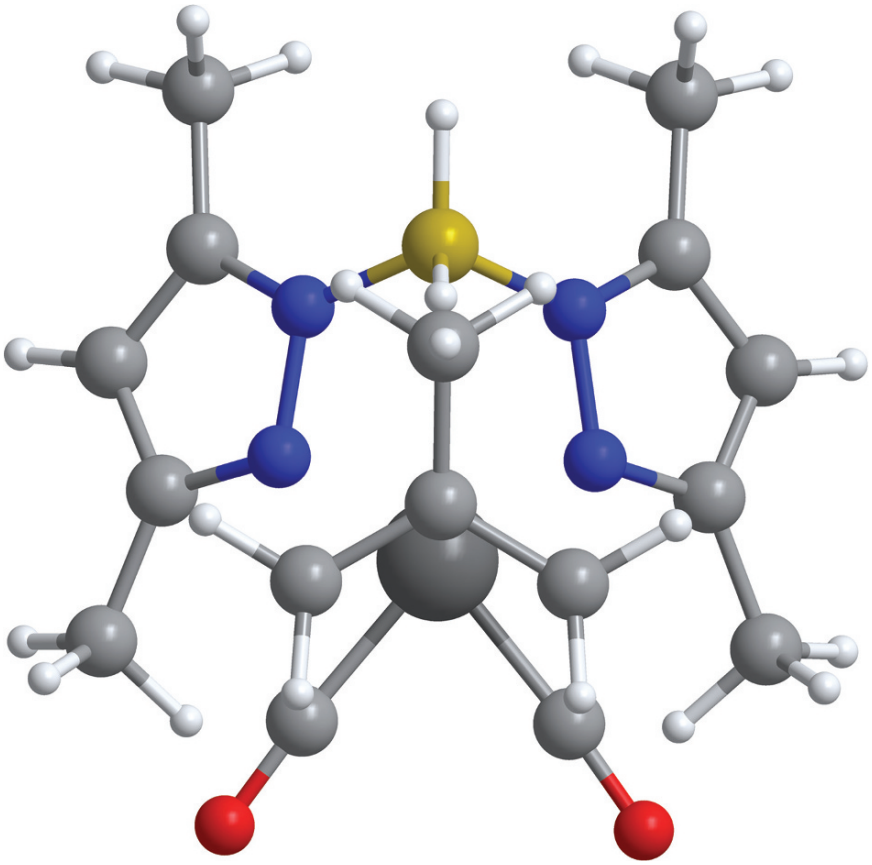
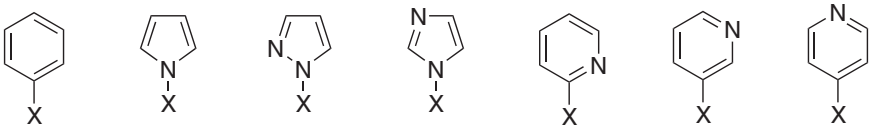


Fig. 5 Compound **160**

represented in Fig. 5, dicarbonyl[dihydrobis(3,5-dimethylpyrazol-1-yl)borato [η-(1,2,3)-2-methylpropen-1-yl]-molybdenum (**160**), there is a fluxional process that exchanges some ligands [153]. The ^{13}C NMR signals observed at low temperature have been assigned thanks to B3LYP/LANL2DZ level calculations including GIAO absolute shieldings (σ).

An aspect directly related to calculated absolute shieldings are Schleyer's NICS (nucleus independent chemical shifts) [10–12]. They are used generally in aromaticity studies, and in our case in heteroaromaticity. We carried out a theoretical study of the monosubstitution effects of all the atoms of the second and third row of the periodic table (X = H, Li, BeH, BH_2, CH_3, NH_2, OH, F, Na, MgH, AlH_2, SiH_3, PH_2, SH, Cl) on the phenyl **161** and pyrrole rings **11** by means of B3LYP/6-31+G(d,p) DFT calculations [26]. All geometric and electronic properties, calculated using the AIM methodology, were analyzed. Some of the results were rationalized based on the electronegativity of the substituents. In addition, the

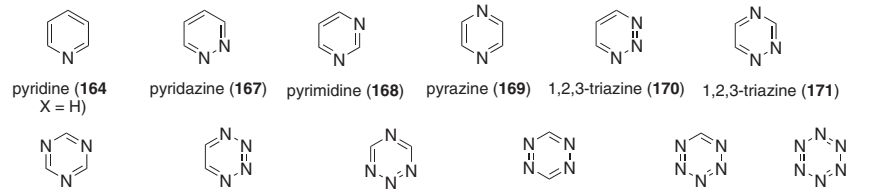
different parameters obtained were compared with different aromaticity indexes (HOMA, NICS, and ASE) as well as with Taft's σ^0_R parameter. We extended these studies to pyrazoles **162** and imidazoles **163** [154]. In the case of heteropentalenes aromaticity (Sect. 6.3), the NICS were used as a criteria.



161 **11** **162** **163** **164** **165** **166**

A theoretical study of the monosubstitution effects of all the atoms of the second and third row of the periodic table on the α, β and γ positions of neutral (**164**, **165**, **166**) and protonated pyridine has been carried out by means of B3LYP/6-31+G(d,p) DFT calculations [155].

Nucleus independent chemical shifts (NICS), aromatic stabilization energy (ASE), and isotropic magnetic susceptibilities, calculated with B3LYP at the 6-311+G (d,p) basis set, were used to evaluate the aromaticity of a set of 12 six-member planar π-electron aromatic systems: mono- and multisubstituted benzenes by nitrogen atoms [156]. NICS were calculated at the center of the rings [NICS(0)], 0.5 and 1 Å above the molecular plane; in order to best reflect π-electron effects, the values of NICS(0.5) were selected. A statistical analysis of the results revealed significant correlations among the above three criteria. The comparison result was benzene > mono-nitrogen benzene **164** (X = H) > di-nitrogen benzene **167**–**169** > tri-nitrogen benzene **170**–**172** > tetra-nitrogen benzene **173**–**175** > penta-nitrogen benzene **176**. The authors found that benzene and hexazine (**177**) are not planar, a known artifact [157] that shed some doubts about the validity of their calculation.



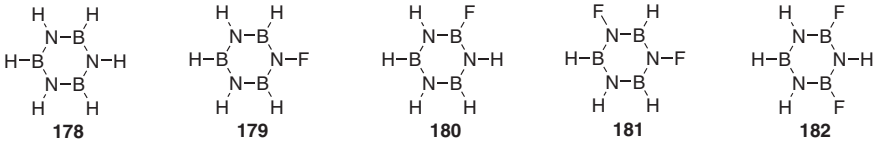
pyridine (**164** X = H) pyridazine (**167**) pyrimidine (**168**) pyrazine (**169**) 1,2,3-triazine (**170**) 1,2,3-triazine (**171**)

1,3,5-triazine (**172**) 1,2,3,4-tetrazine (**173**) 1,2,3,5-tetrazine (**174**) 1,2,4,5-tetrazine (**175**) pentazine (**176**) hexazine (**177**)

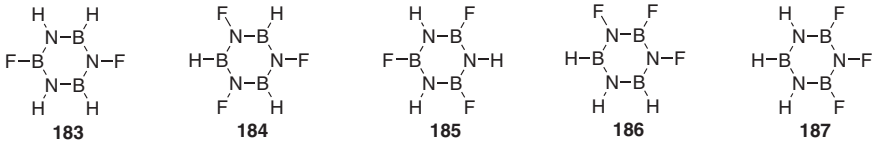
5.3 NMR J

The difficulty in calculating coupling constants is much more than for calculating chemical shifts for the same requirements of accuracy. On the other hand, the structural information is equally relevant. Our contribution to this important topic can be

classified in two parts, depending on the method used. In collaboration with Janet E. Del Bene we have been using EOM-CCSD (equation-of-motion, coupled-cluster singles and doubles) a method due originally to Perera and Bartlett [158–161]. For the most part, these studies concern coupling constants through hydrogen bonds (the so-called ^{nh}J) [162] but we have made some contributions to the field of aromatic heterocycles.

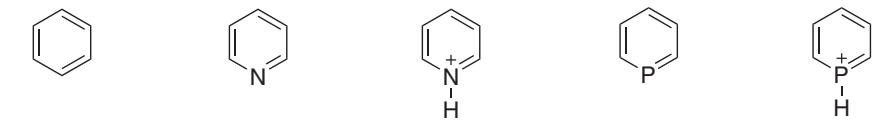


178 **179** **180** **181** **182**



183 **184** **185** **186** **187**

The aromaticity of borazines has been the subject of many studies [163–167]; our contribution was to study the compounds of above structure. For molecules in which F atoms are not bonded to adjacent atoms in the ring, such as **181**–**185**, fluorine substitution increases the one-bond ^{11}B–^{15}N coupling constants involving the atom at which substitution occurs but leaves the remaining one-bond B–N coupling constants essentially unchanged. For these molecules, the magnitudes of one-bond B–N coupling constants are only slightly dependent on the number of F atoms present. Fluorine substitution at adjacent B and N atoms in the borazine ring further increases the one-bond B–N coupling constant involving the substituted atoms and has the same effect on the other one-bond coupling constants, as observed for corresponding molecules in which substitution occurs at alternate sites. In contrast to the effect of F substitution, substitution of Li at either N or B decreases one-bond B–N coupling constants relative to borazine. The effects of F and Li substitution on one-bond B–N coupling constants for borazine are similar to F and Li substitution effects on ^{13}C–^{13}C coupling constants for benzene [168].



161 (X = H) **164** (X = H) **188** **189** **190**

We carried out ab initio EOM-CCSD calculations to evaluate one-, two-, and three-bond ^{13}C–^{13}C, ^{15}N–^{13}C, ^{31}P–^{13}C coupling constants in benzene (**161**), pyridine (**164**, X = H), pyridinium (**188**), phosphinine (also called phosphabenzene and λ^3-phosphorin) (**189**), and phosphininium (**190**). The introduction of N or P heteroatoms into the aromatic ring not only changes the magnitudes of the corresponding

X–C coupling constants (*J*, for X = C, N, or P) but also the signs and magnitudes of the corresponding reduced coupling constants (*K*). Protonation of the heteroatoms also produces dramatic changes in coupling constants and, by removing the lone pair of electrons from the σ-electron framework, leads to the same signs for the corresponding reduced coupling constants for benzene, pyridinium, and phosphininium. C–C coupling constants are rather insensitive to the presence of the heteroatoms and protonation. All terms that contribute to the total coupling constant (except for the diamagnetic spin-orbit, DSO, term) must be computed if good agreement with experimental data is to be obtained [169].

We have also calculated coupling constants using other DFT methods such as that described by Peralta et al. [170, 171]. Thus, we have calculated the 243 coupling constants (involving ^{1}H, ^{13}C, and ^{15}N nuclei) of eight *N*-X-pyrazoles [**162**, R = H, CH_3, C_6H_5, $COCH_3$, NH_2, NO_2, SO_2CF_3, $Si(CH_3)_3$] and compared them with 131 experimental values [172]. The whole collection has been statistically analyzed and the agreement, being good, can be used to estimate new couplings. This study proves that at the B3LYP/6-311++G** computational level most coupling constants of pyrazoles are well reproduced. The exceptions are the $^{1}J_{CC}$, but even for these, the experimental and calculated values are linearly related.

5.4 MW Spectroscopy

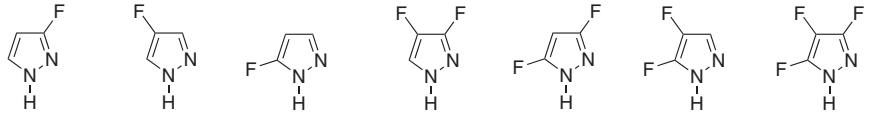
One of our rare incursions into the field of microwave spectroscopy concerns 1-nitropyrazole (**162**, X = NO_2). MP2/6-31G* calculations reproduce very well the experimental geometry [172, 173] and the calculated rotational constants of a series of pyrazoles (in MHz) were reported (**155**, X = H, BH_2, BH_3^-, CH_3, CHO, CF_3, NH_2, NO_2, OH, AlH_2, SiH_3, PH_2, SO_2H, *N*-oxide). Our other contributions deal with simple molecules [174].

6 Special Heterocycles

6.1 Fluorinated Derivatives

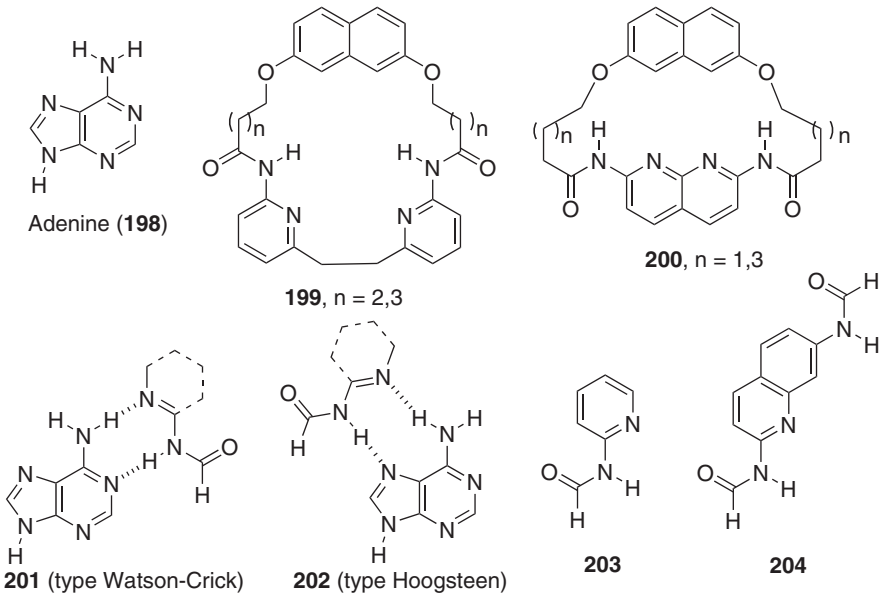
Fluorine is a very important atom both for the biological applications of fluorinated heterocycles [175, 176] and for ^{19}F chemical shifts and the large coupling constants with ^{19}F [177]. We have already discussed the case of fluoroindazoles, **44**–**46**) [51] and we have published a paper reporting MP2/6-311G** calculations of all *C*-fluoropyrazoles **191**–**197**. The order of stability of monofluoropyrazoles is 3-F (**191**) > 5-F (**193**) > 4-F (**192**), and that of difluoropyrazoles is 3,5-diF (**195**) > 3,4-diF (**194**) > 4,5-diF (**196**). This corresponds to the predominance of 3-fluoro substituted annular tautomers **191** and **194** over the 5- substituted ones, **193** and **196**, by about

15 kJ mol^{-1} [178]. In the same paper we reported the calculated ^{1}H, ^{13}C, ^{15}N, and ^{19}F absolute shieldings of compounds **191**–**197**, which show excellent agreement with the experimental chemical shifts.



6.2 Nucleotides

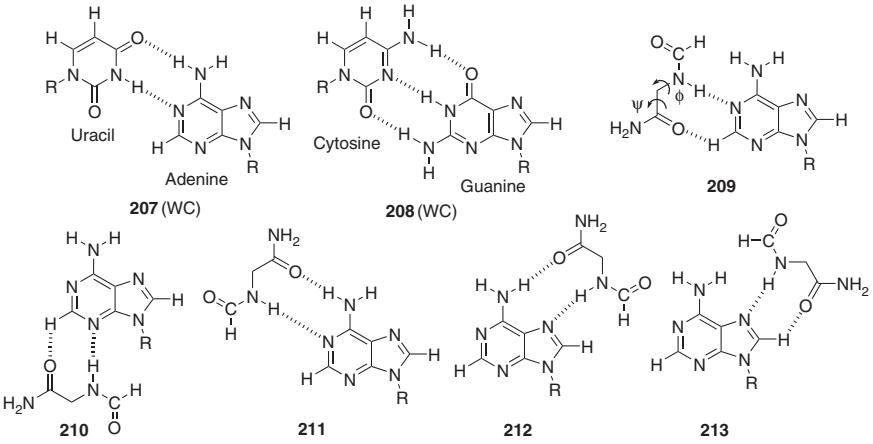
As aromatic heterocycles are part of amino acids (pyrrole, indole) and nucleic acids it is normal that some aspects of the latter compounds have been the subject of some of our studies [179–182].



We have modeled the interaction of adenine (**198**) with synthetic receptors **199** and **200** assuming Watson–Crick (WC) **201** and Hoogsteen **202** interactions [179]. The receptors were replaced by simpler models, **203** and **204**, for the B3LYP/6-31+G** calculations. The different binding modes between pyridine **203** and 1,8-naphthyridine **204** derivatives with adenine were compared to those of the latter with uracil and cytosine. The dispositions of the calculated complexes indicate that the synthetic receptors with two pyridine moieties are able to interact simultaneously with two different parts of the adenine molecule. In contrast, those receptors

with a 1,8-naphthyridine moiety only are able to interact in one site. The experimental data confirm that the pyridine receptor binds adenine more tightly than the naphthyridine ones.

We have also studied the fundamental problem of the protein–nucleic acid base (NAB) interaction [180]. We carried out a theoretical study of the complexes due to hydrogen bond (HB) formation of a protein backbone model, *N*-formylglycinamide (For-Gly-NH_2, 2-formylaminoacetamide, Fig. 6) in β (**205**) and γ conformations (**206**), with the isolated NABs as well as with AU, GC dimers in WC disposition. Only those dispositions with a double HB between the protein model and the nucleic acid bases were considered. The aromatic CH groups of the nucleic acids were included as HB donor (complexes with adenine A: **208**–**212**). The results indicate that the strongest HB between the individual NAB and the protein models involve the atoms that participate in the formation of the WC dimers. In the trimeric complexes, no significant preference is obtained for the **207**–AU trimers studied. However, in the **207**–GC complexes, the one where formylglycinamide interacts with the carbonyl group of guanine and the amino of cytosine simultaneously is favored. The electron density of the complexes was analyzed using the AIM methodology, finding exponential relationships between the electron density and its Laplacian vs. the bond distance. The effect in the nuclear chemical shielding due to the complexation was also explored. Exponential relationships were found for the variation of the chemical shift of the ^{1}H signal for the NH–O and NH–N interactions vs. the HB distance.



We have studied theoretically (B3LYP/6-31+G**) all the possible complexes formed by the double interaction established between RNA bases and guanidinium and formate ions, as a model for the interacting groups of arginine and glutamic or aspartic amino acid side chains (formate anion complexes **214**–**218**) [181]. The range of interaction energies obtained allowed for a distinction between bidentate (**214**, **215**, **217**) and bifurcate hydrogen bond interactions (**209**, **211**). Analysis of the electron density and of the natural bond orbital (NBO) shows that these complexes are bound by double hydrogen bonds established between the donor and acceptor

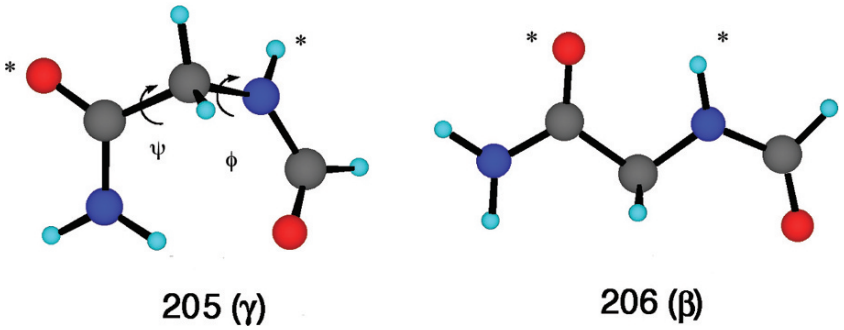
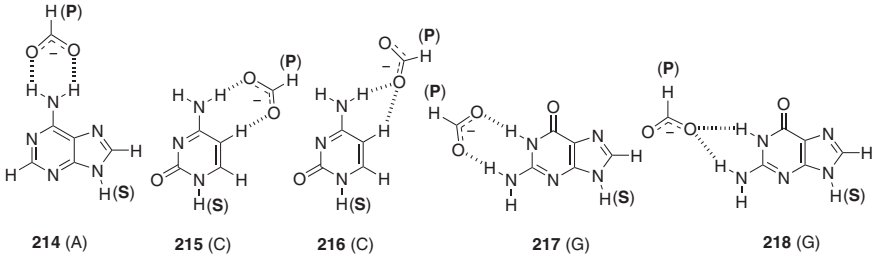


Fig. 6 The γ and β conformations of *N*-formylglycinamide (**205** and **206**). The atoms with the *asterisks* are those considered to form HBs with NAB

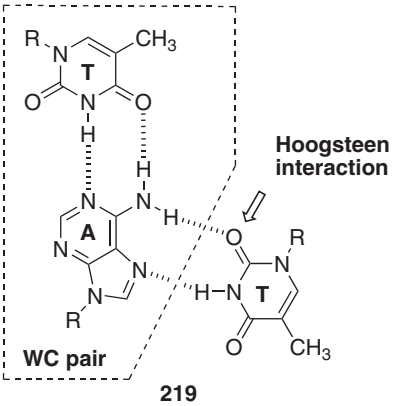
groups of guanidinium and formate, respectively, and those of the RNA bases. We have confirmed that the interactions present are HBs of medium strength, established by the interaction between a lone pair of the HB acceptor and an unoccupied bond orbital of the HB donor. The charge transfer observed in these RNA base–guanidinium/formate complexes is in important agreement with the large interaction energies computed for them. This could be explained by the ionic nature of one of the molecules involved in the complexes, which would reinforce the intermolecular binding forming charge-assisted hydrogen bonds [183, 184]. Good correlations have been found between the logarithm of the electron density at the bond critical point (bcp) and the HB distance as well as between the r(bcp) and the orbital interaction energy. The correlation between electron density and orbital interaction is a very relevant finding since both parameters provide information on the nature and strength of a bond, but from very different sources.



214 (A) **215** (C) **216** (C) **217** (G) **218** (G)

The structures of the bases of these DNA triplexes were studied, by means of B3LYP/6-31+G** calculations, in terms of their interaction energies and electron densities for the different hydrogen bonds established. This is one of the interactions that determines the structure and dynamics of nucleic acid molecules, and some of them, **219** and **220**, are represented in the below structure [182]. A good agreement was found with the experimental results. The trends observed for the interaction energies are consistent with those observed by experimental and/or by

molecular dynamics studies in the case of T.A–T, C+.G–C, and G.G–C. As for G. T–A, the DFT predictions are different than the experimental ones, and this may be due to the absence of stacking effects. The electron analysis results agree rather well with the calculated interaction energies. When a third base is added to a dimer, the strength of the HBs of the dimer becomes modified. These changes in the dimer's HBs provoke modifications in their structures by increasing the distance in the major groove and decreasing the space in the minor groove. This modification in the original double helix may help explain why transcription is inhibited upon triplex formation. The electron density analysis we performed gives insights into the nature of the interactions established among the bases and, therefore, allows a better understanding of the formation of nucleic acid triplexes and how their structure and HB patterns could have biological implications.



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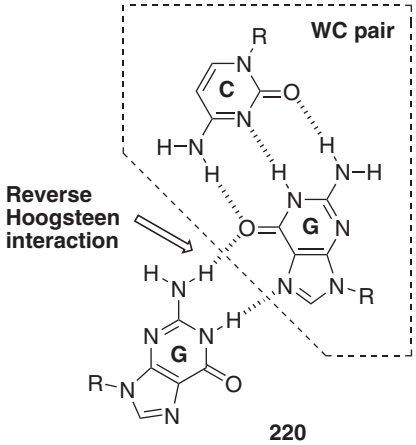
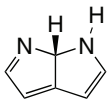


220

6.3 *Heteropentalenes*



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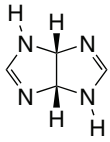
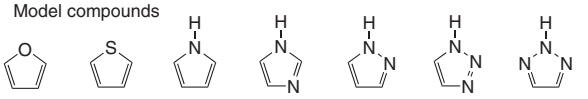


222

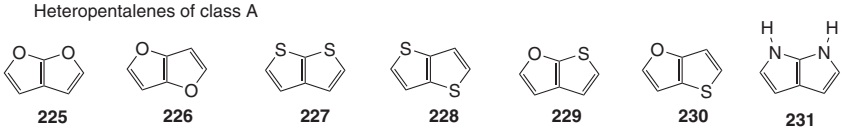
Heteropentalenes, and in particular azapentalenes (containing at least a nitrogen atom), are a fascinating family of aromatic compounds, which we studied in detail a long time ago [185]. Recently, in our studies on chiral recognition [186], we have used as models reduced azapentalenes **221** [187] and **222** [188]. This led us to study the aromaticity of a series of related azapentalenes belonging to the family of azapentalenes lacking nitrogen heteroatoms in the ring junction (Class A, **225**–**240**). Some model compounds (**223**, **224**, **10**, **3**, **87**, **30a,** and **30b**) were necessary for the comparisons.

Model compounds

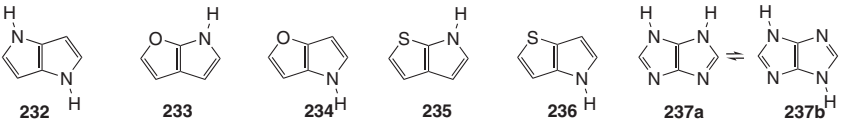


223 **224** **10** **3** **87** **30a** **30b**

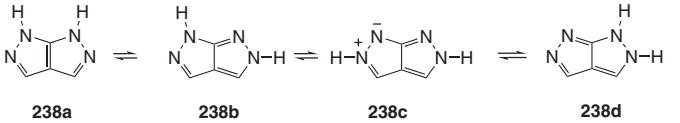
Heteropentalenes of class A



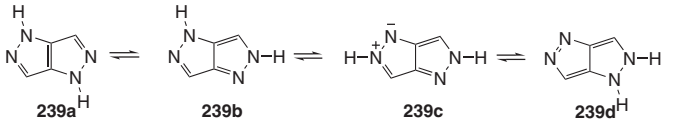
225 **226** **227** **228** **229** **230** **231**



232 **233** **234** **235** **236** **237a** **237b**



238a **238b** **238c** **238d**



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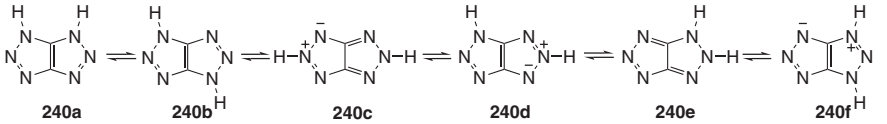

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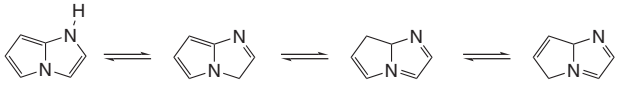

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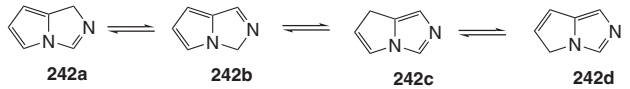

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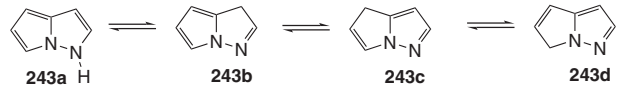
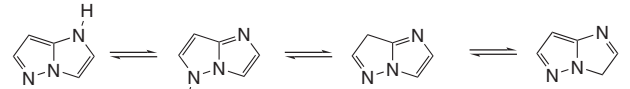


243a **243b** **243c** **243d**



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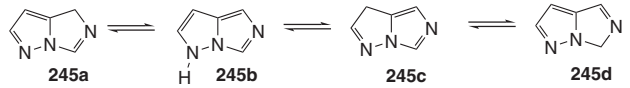
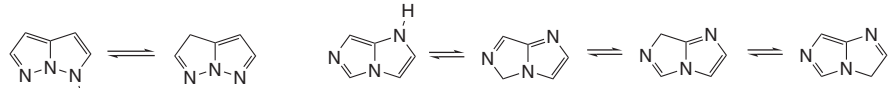


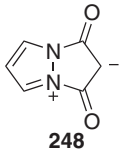
245a **245b** **245c** **245d**



246a **246b** **247a** **247b** **247c** **247d**

Theoretical calculations at the B3LYP/6-311++G** level including GIAO and NICS chemical shifts have been carried out on seven simple heterocycles and 28 heteropentales (22 of them being azapentalenes **237**–**240**). The relative energies are discussed as a function of the heteroatoms and of the topology ([2,3-*b*] vs. [3,2-*b*]) for isomers and tautomers. Schleyer's NICS(0) and NICS(1) (see Sect. 5.2) were used to discuss the aromaticity of these compounds. In this work we have covered a field that is still neglected: the aromaticity of azapentalenes derived from imidazoles, pyrazoles, and 1,2,3-triazoles. We have also completed the study of heteropentalenes containing O and S atoms. It comes as no surprise that energetic and magnetic criteria, without being orthogonal are, nevertheless, quite different.

We have devoted two other papers to heteropentalenes, one to azapentalenes with one ring junction nitrogen atom (B series) and the other to azapentalenes with two ring junction nitrogen atoms (C series) (unpublished results from this group). In the first case we have focused our attention on tautomerism and aromaticity (energies and NICS).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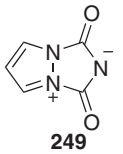
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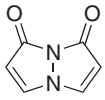
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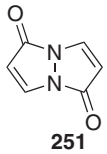
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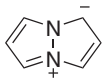
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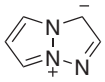
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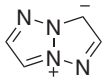
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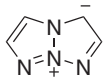
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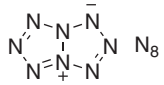

256

In the last series of azapentalenes (the less experimentally known) we have studied bimanes (**248**–**251**) [189, 190] and mesoionic derivatives **222**–**246**. Only the last compound **256**, being a polymorph of dinitrogen, has been studied much [191–201]. We have calculated (Fig. 7) the molecular electrostatic potentials (MEPs) of compounds **222** and **256** [202].

6.4 Other

We have published some papers concerning some less common heterocycles such as 1,2,4-diazaphospholes **257** and **258** [203]. Using X-ray crystallography, CPMAS NMR, and GIAO-type calculations we have found that **257** is a cyclic dimer with localized N–H protons (similar to pyrazole dimers) while **258** is probably a tetramer (similar to pyrazole tetramers) showing ISSPT (intramolelecular solid state proton transfer). This prediction was only partly true because **258** crystallizes in two cyclic dimers, both presenting proton disorder [204] (Fig. 8).

It is known that the last molecule represented on Pauling's chalkboard (1994, preserved to this day by his friends) was the azide derivative **259** [205–207] of

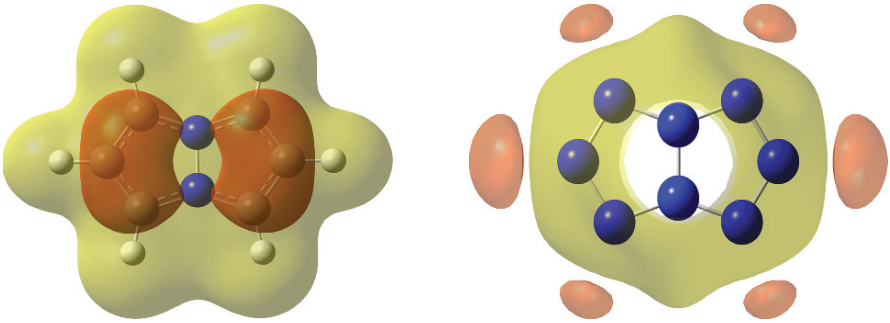
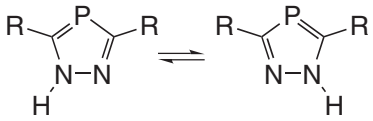


Fig. 7 Molecular electrostatic potentials (MEP) of compounds **252** (*left*) and **256** (*right*). *Yellow* and *brown* parts correspond to positive and negative regions, respectively



257, R = *t*-Bu
258, R = Ph

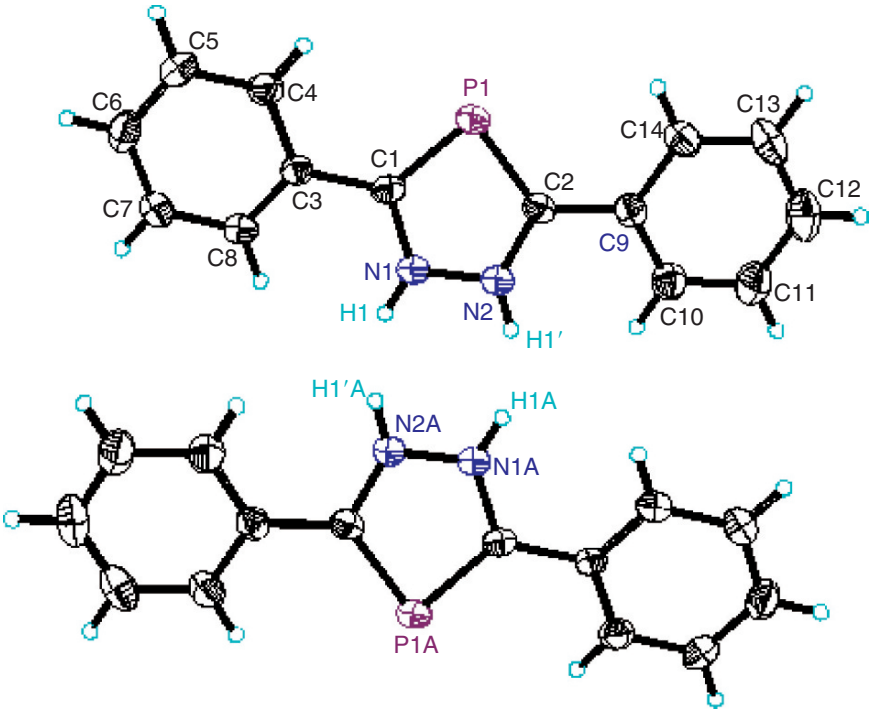
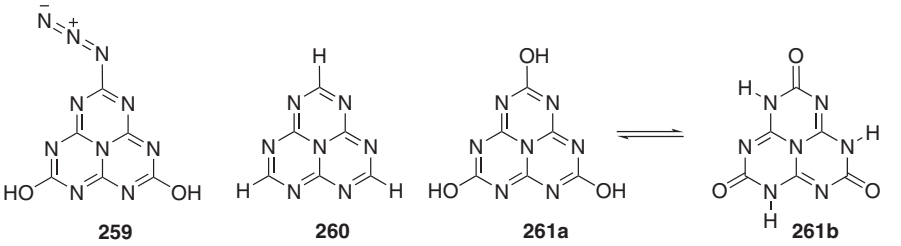


Fig. 8 X-ray structure of one of the dimers of **258**

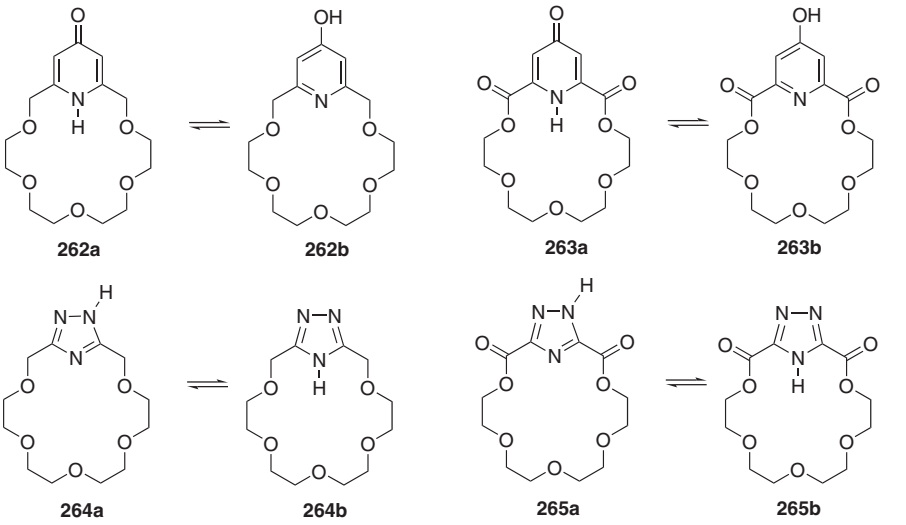
tri-*s*-triazine **260** (1,3,4,6,7,9,*9b*-heptaazaphenalene or cyamelurine). We decided to theoretically study cyameluric acid (1,3,4,6,7,9,*9b*-heptaazaphenalene-2,5,8 (1*H*,3*H*,6*H*)-trione, **261a**) and its possible tautomeric structures [208]. Not considering the orientation of the OH group, compound **261** can exist in 17 tautomeric forms: one tri-hydroxy, three di-hydroxy, four tri-oxo, and nine mono-hydroxy. B3LYP/6-31G* results indicate that the most stable tautomer corresponds to the tri-oxo form (**261b**). We have also studied the singular case of borazine [168].



7 Supramolecular and Macrocycles

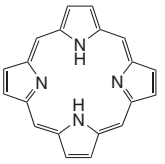
We have already reported the case of macrocycles **200** and **201** and we will discuss other papers dealing with supramolecular structures involving macrocycles. Note that all the HB complexes discussed so far are supramolecular systems.

Thus, we have studied theoretically the tautomerism of pyridones and 1,2,4-triazoles related to two crown ethers and two crown esters derived from these heterocycles [209]. For the four macrocycles **262–265**, Bradshaw identified a single tautomer by X-ray crystallography [210–213]. To rationalize these findings, a series of calculations from simple models to crown derivatives were carried out. The most interesting case concerns the observation, for the first time, of a 4*H*-1,2,4-triazole tautomer **265b**.



To explain this result (remember that 4*H*-triazoles **60c** are much less stable than 1*H* (**60a** and **60b**) it was necessary to calculate the whole crown ester plus a caged water molecule.

Structural, energetic, and electronic aspects of a series of porphyrins and related compounds in their neutral, anion, and dianion electronic states were studied by means of DFT calculations [B3LYP/6-31+G(d,p)]. The analysis of the electron density put forward a number of different kinds of interactions between the inner atoms. Intramolecular correlations similar to the ones found in intermolecular N–H···N interactions have been found [214].



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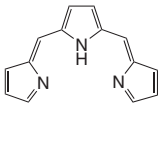

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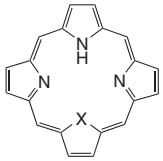
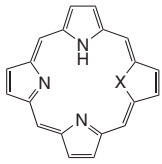


268
(X = O, S, Se)



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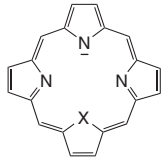
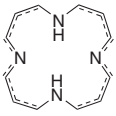


270
(X = O, S, Se)



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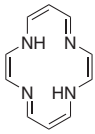

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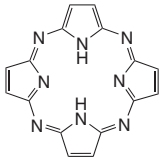

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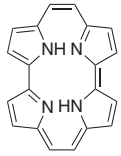


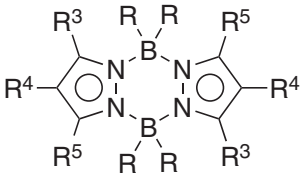
274

A theoretical study of the acidity (proton loss) of the porphyrin **266** and some related systems was carried out by means of the B3LYP/6-31+G(d,p) computational level. These include, on one hand, porphyrin fragments **267** and pyrrole **11** (X = H) and the monoanion and dianion of **266** and, on the other hand, chalcogen-related porphyrins **268**, **269**, and **270** and their anions, as well as cyclic nitrogen derivatives **271**, **272**, **273**, and **274**, simplified models of porphyrin, dibenzo[14]annulene, phthalocyanine, and porphycene.

Analysis of the electron density indicates the presence of a large number of different interactions between the atoms of the inner part of the systems considered, for instance, chalcogenic interactions between sulfur (or selenium) and the opposed N atom anion. Special emphasis was put on acid–base equilibria (neutral/anion/dianion). The relationship between the electron density and the Laplacian at the bcp indicate that these interactions are similar to those encountered in intermolecular interactions, to the point that they can be analyzed together.

The aromaticity of the different tautomers of compound **263** has been studied comprehensively by García de la Vega at the density functional theory level, using double-zeta double-polarized basis sets [215]. Using geometry-based index HOMA and magnetic properties-based NICS, the aromaticity of the whole rings and the different contours was evaluated.

Pyrazaboles **275** (compound **276** is a particular example of **275** with $R^3 = R^5 = H$) were discovered by Trofimenko [216, 217] and thoroughly studied by Niedenzu



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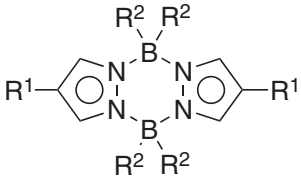

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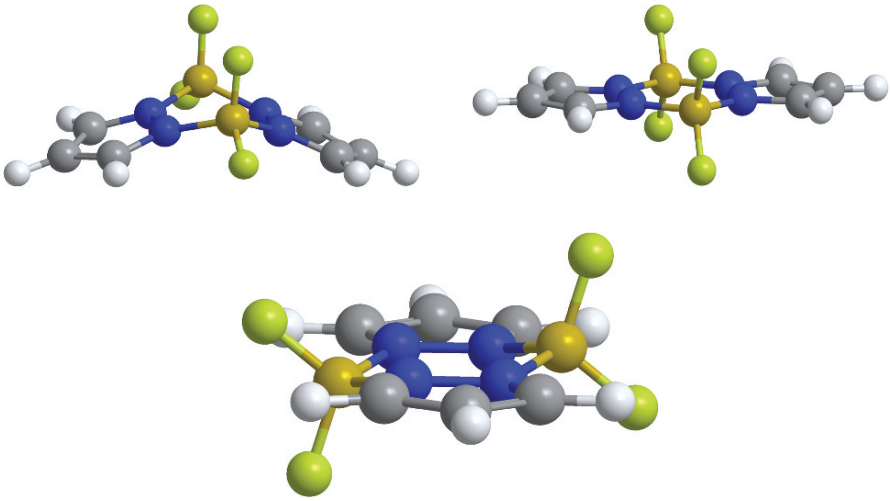
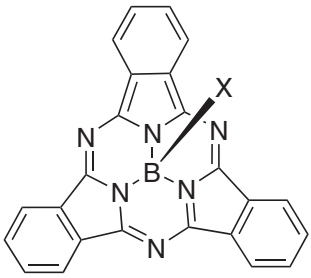


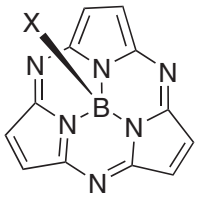
Fig. 9 Boat (*left*), chair (*middle*), and planar (*right*) conformations of pyrazabole **276** (R^1 = H, R^2 = F)

[218, 219]. We have studied compounds **276** (R^1 = H, I, CCH; R^2 = H, F) [220], concentrating on what affects their conformation (Fig. 9).

Theoretical calculations (B3LYP/6-311+G** and MP2/6-31G* computational levels; in the case of iodine derivatives, the calculations were carried out at the B3LYP/DGDZVP level) show that all the studied pyrazaboles **276** have a boat conformation as an energy minimum, with the planar and chair conformations as transition states in an energy diagram. The boat conformation has a molecular dipolar moment in the direction of the bend angle; therefore these molecules could be of interest in the preparation of new bent polar materials. Analysis of the calculated NMR chemical shifts and comparison with the experimental NMR data leads to the conclusion that in solution all compounds are in a boat conformation with a rapid boat-to-boat inversion on the NMR timescale. In the solid state (X-ray crystallography) all BH_2 compounds are bent in shape. However, in the case of the BF_2 compounds we obtained both bent and planar conformations depending on the substituents, indicating that substitution at the boron, stacking effects, and short contact interactions are decisive in terms of the molecular structure.



277 (SubPc)



278 (SubPz)

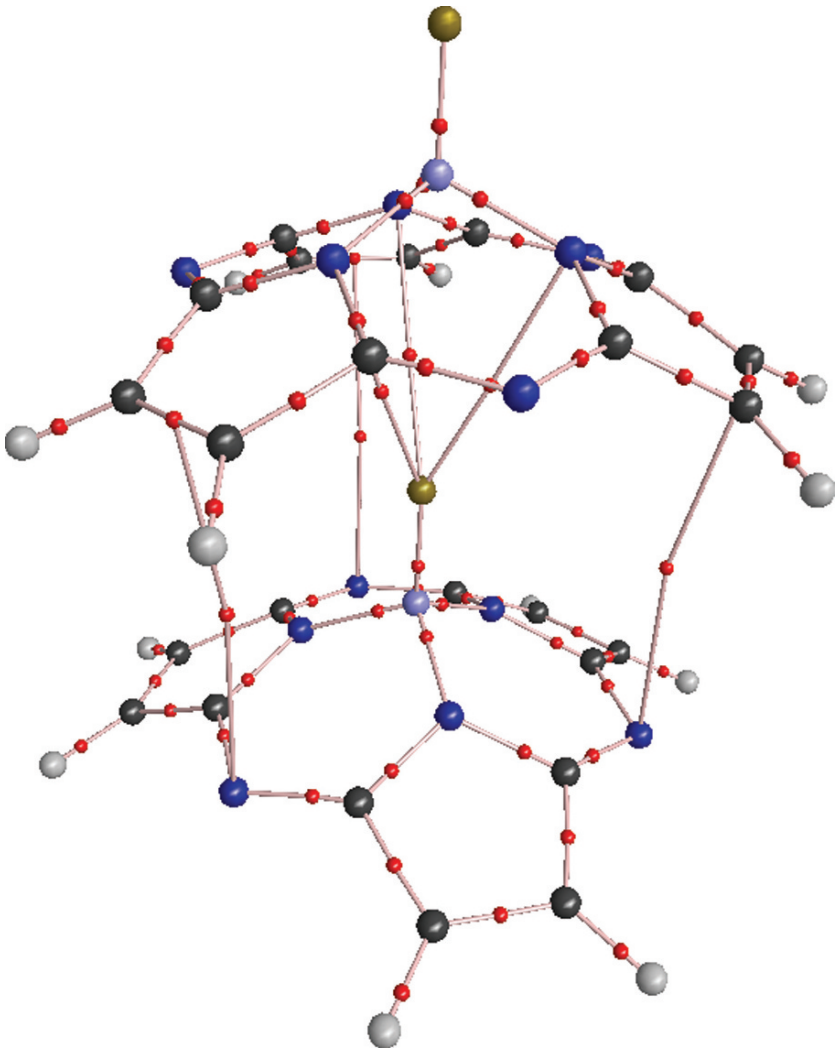


Fig. 10 Molecular graph of the fluorosubazaporphyrin dimer (**278**, X = F)$_2$. The bond critical points and bond paths are represented

Aromatic or π-conjugated curved compounds have been the subject of many theoretical and experimental studies in recent years as a consequence of their intriguing chemical and physical properties [221, 222]. Among them, subazaporphyrins [223–227] (SubPcs and SubPzs) are heteroaromatic chromophores that constitute lower homologs of tetraazaporphyrins (phthalocyanines and porphyrazines) in that they are made of three instead of four *N*-fused 1,3-diiminoisoindole or 2,5-diiminopyrrole units, respectively. These kinds of macrocycles have been known since the 1970s [228]. Compound **278** (X = F) crystallizes to form columns that we have modeled, calculating up to a tetramer (B3LYP/6-311++G** calculations).

Analysis of the electron density of the dimer sheds some light about the nature of the intermolecular interactions that produce such a drastic shortening in the distances between macrocycles within a column. Thus, the arrangement of the SubPz **278** (X = F) into columnar crystalline structures implies more than a simple p-stacking along the *c* direction but also the presence of three bcps between the fluorine atoms of one of the molecules and the fluorosubazaporphyrin that is above. In addition, three bcps are found that can be associated to π–π interaction between the two molecules (Fig. 10).

8 Conclusions

In this review we have tried to summarize our contribution to heteroaromaticity, which is essentially based on the use of theoretical methods. In the future it is expected that more and more elaborate methods will shed light on the properties of aromatic heterocycles, allowing the creation of a rational picture of them. At the limit, one can forecast a day where the teaching of this part of chemistry will be based on computed properties.

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Aromaticity of Six-Membered Rings with One Heteroatom

A.T. Balaban

Abstract Six-membered rings with one heteroatom are aromatic when there is a continuous conjugation involving six delocalized electrons. The main-group heteroatom from groups 16–13 of the periodic system can be (ordered approximately according to decreasing electronegativity): O^+, S^+, Se^+, Te^+, NR^+, N^+–O^-, N, P, PR_2, As, Sb, Bi, SiR, GeR, BR^-, and GaR^-. Among elements that give rise to aromatic metallabenzenes, so far most investigations have concentrated on Os, Ir, Pt, and Rh. Various qualitative and quantitative aspects of aromaticity are reviewed, such as chemical reactivity, molecular geometry, energetics, and magnetic features.

Keywords aromaticity, arsabenzene, boratabenzene, germabenzene, heterocycles, metallabenzene, phosphabenzene, pyridine, pyridinium, pyrylium, silabenzene, thiopyrylium

Contents

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Abbreviations

ANRORC	Attack by nucleophile, ring opening, ring closure
DFT	Density functional theory
DNA	Deoxyribonucleic acid
EN	Term in HOMA due to the bond length alternation
EWG	Electron withdrawing group
GEO	Term in HOMA due to the bond elongation
HOMA	Harmonic oscillator model of aromaticity
HOSE	Harmonic oscillator stabilization energy
IUPAC	International Union of Pure and Applied Chemistry
NICS	Nucleus independent chemical shift
NMR	Nuclear magnetic resonance
NRT	Natural resonance theory
RE	Resonance energy
RNA	Ribonucleic acid
Tbt	Tris[bis(trimethylsilyl)methyl]phenyl

1 Introduction

Aromatic compounds are important for chemistry in general, representing numerically about half of the 30million registered chemical structures, the vast majority of which are based upon carbon and hydrogen, i.e., are organic compounds. Earlier, many aromatics were obtained as side-products from coal tar resulting during the conversion of coal into coke, but nowadays huge chemical industries are based on converting alkanes from petroleum into benzene, toluene, styrene, and other aromatic hydrocarbons. Plastics, synthetic rubber, and most of the dyestuffs use large amounts of these hydrocarbons either directly, or after converting them into phenols, amines, etc. Among all aromatic compounds, heterocycles represent more than two thirds and allow the most diverse properties and uses. A very brief enumeration of what aromatic heterocycles do for our biology should include the photosynthesis catalyzed by chlorophyll, the transport of oxygen and carbon dioxide by hemoglobin in blood, the essential amino acids histidine and tryptophan, the storage and delivery of chemical energy via ATP, the five nucleic bases of the universal genetic code (A/U, C, G, and T in DNA and RNA), many coenzymes and vitamins, and most medicinal drugs, dyes, and organic conductors.

The importance of aromatic heterocycles for life and society [1], as well as for chemistry and the chemical industry, has led to the recent publication of several books, book chapters, and journal reviews [2–10], including *Comprehensive Heterocyclic*

Chemistry I and II. The third updated series of *Comprehensive Heterocyclic Chemistry* III and the present monograph are both published in 2008.

The present chapter deals only with a small part of the large body of aromatic heterocycles, and cannot be exhaustive in the literature coverage. We shall try to provide a partial answer to the question of which from all the possible six-membered rings with one heteroatom have been selected by evolution of life (one may mention the biologically important NAD–NADH system). It is now well established that the only six-membered aromatic rings with one heteroatom that are stable towards air and humidity under normal conditions (similarly to benzene) have heteroatoms belonging to groups 16 and 15 of the periodic system. For most of the needs of living organisms, natural evolution cherished monocyclic five- and six-membered nitrogen-containing heterocyclics, and bicyclic condensed systems formed from them or from benzo-annelated congeners. In addition, most of the colors of the vegetal kingdom are due to benzo[*b*]pyrylium cations of anthocyanins. Thus, only nitrogen and oxygen are the heteroatoms selected by natural evolution, although thiopyrylium, selenopyrylium, phosphabenzene, and arsabenzene have sufficient stability.

It has been a well-entrenched dogma that elements beyond argon are reluctant to form multiple covalent bonds, citing as examples the difference between CO_2 and SiO_2. One should note, however, that the formation of multiple bonds for such atoms occurs with increasing relative easiness in the order Si < P < S; indeed, although silabenzene is unstable under normal conditions, phosphabenzene and thiopyrylium are normal, stable aromatic systems.

To adopt the nice metaphor of Frenking and Krapp [11], aromaticity is a unicorn (a useful mystical animal that everybody is familiar with, although nobody has seen one). It should not be doomed to extinction (as proposed earlier) because if it is tamed, it brings law and order in an otherwise chaotic and disordered world.

About 150 years ago, in a flash denoting a genius's power of generalization, Kekulé proposed a structure for the puzzle raised by the chemical composition and chemical behavior of benzene. This compound had been discovered by Faraday and for 40 years this hydrogen-poor hydrocarbon did not align itself to other hydrogen-poor compounds (alkenes, dienes, alkynes) that underwent readily addition reactions, but behaved like the hydrogen-rich alkanes that reacted by substitution. With postulates that were as bold as those that Bohr would introduce during the next century in his atomic model, Kekulé visualized aromaticity as a structural feature, and thereby opened a vast field of experimental facts that would be later be accommodated in the comprehensive theory of quantum mechanics, unifying physics with chemistry. Two converging theoretical approaches, namely the valence bond and molecular orbital methods, revealed the special type of planar electronic delocalization that characterizes benzene and its congeners. A few historical details are supplied in Table 1. The contributions of Armit and Robinson (anticipated by Crocker, as explained in [12]), Pauling, Erich Hückel, and Clar deserve special mention for becoming rapidly adopted by chemists dealing with aromatic systems.

The fact that sp^2-hybridized C–C bonds prefer the honeycomb bond angles of 120° contributes to the exceptional stability of benzene and graphite. Hückel's rule stipulates that aromaticity is associated with a cyclic conjugated system of $4n + 2$

Table 1 Significant moments in the history of aromaticity till 1970

Name	Year	Achievement
	<1800	Isolation of natural compounds with various aromas
Faraday	1825	Isolation of benzene (illuminating gas condensate)
Anderson	1849	Discovery of pyridine in bone pyrolysis products
Perkin Jr.	1856	Patent for the manufacture of mauvein
Griess	1858	Diazotization of aniline derivatives, azo dyes
Kolbe	1860	Synthesis of salicylic acid
Kekulé	1865	Benzene formula, aromaticity as structural feature
Erlenmeyer	1866	Naphthalene formula, aromaticity as reactivity
Baeyer	1864	Synthesis of barbituric acid
Hantzsch	1882, 1888	Synthesis of pyridine, thiazole
Meyer	1883	Isolation of thiophene
Bamberger	1891–1893	Pre-sextet formulas for five-membered heterocycles
Fischer	1899	Synthesis of purine
Willstätter	1911	Proof that cyclooctatetraene is not aromatic
Arndt	1924	Electronic delocalization in pyrones
Robinson	1925	Electron sextet
Ingold	1926	Mesomerism
Pauling, Wheland	1930	Resonance, valence bond theory
Pauling	1931	Hybridization, electronegativity
Hückel	1931	Molecular orbital theory, $4n+2$ π-electron rule
Pauling	1936	Paramagnetic susceptibility, magnetic anisotropy
Dewar	1952, 1965	Tropolones, Dewar resonance energy
Doering	1954	Tropylium salts
Huisgen, Ugi	1956	Synthesis of fairly stable pentazoles
Clar	1957–1960	Spectra of acenes, aromatic sextet rules
Breslow	1958	Cyclopropenylium salts
Pople	1958	NMR chemical shifts, ring current
Albert	1959	Bond length equalization
Sondheimer	1962	Annulenes with >10 carbon atoms
Vogel	1964	Methano[10]annulene
Boekelheide	1970	Bridged[14]annulenes

π-electrons, with n being an integer starting with 0 [in more mathematical terms 2(mod4)]. In comparison with other monocyclic aromatic $(CH)_{2k}$ systems (annulenes), benzene has the largest delocalization energy per electron. It is only more recently that Hiberty and Shaik have pointed out the relative contributions of σ- and π-electrons of benzene by showing that there is a tug-of-war competition between the σ-electron framework, which has an energy minimum at equal bond lengths, and the π-electrons, which prefer energetically the alternating bond lengths. The bond length equalization in benzene is therefore due to the σ-electrons, but the aromatic reactivity is due to the high polarizability of the π-electrons that provide the frontier orbitals [13].

The present review will be based on the "classical" views of aromaticity [14–16], confining it to two dimensions, although it has been customary to ascribe the exceptional stability of icosahedral *closo*-carboranes to their three-dimensional aromaticity [17, 18]. The discovery of fullerenes, nanocones, and nanotubes has opened new vistas for "bent and battered" benzene rings. Also, it is possible to obtain benzenic rings

with alternating bond lengths by annelation with three bicyclic ring systems [13]. One should not enlarge the realm of aromaticity by including "hyphenated aromaticities" (pseudo-aromatic, quasi-aromatic, etc.).

2 Aromaticity: A Fuzzy Yet Extremely Useful Concept

The main structural characteristics of "classical" aromatic systems are: continuous conjugation of π-electrons, filled bonding orbitals, absence of non-bonding orbitals, and no occupied anti-bonding orbitals. Consequently, energetic, geometric, and magnetic features (along with stability and characteristic chemical reactivity, which have nowadays a lesser role than in the past) are widely accepted characteristics for aromatic systems. Each of these features served as basis of various scales of determining quantitative measures of aromaticity. Here we will mention only a few of these, but the reader may consult the bibliography for additional data. Among energetic criteria [8, 9, 15, 19], one has theoretical resonance energies (RE, such as empirical, Dewar's, the Hess-Schaad RE, or the topological RE) and experimentally determined heats of combustion from which one can compute heats of formation by means of homodesmic and superhomodesmic reactions. Geometrical criteria (the Julg index [20], the Jug index [21], and especially the Bird index [22–26] and the Krygowski HOMA index [27–30]) are based on the assumption that experimentally determined bond distances (by means of X-ray diffractometry) reflect electronic delocalization by the corresponding bond equalization. The revised HOMA index has also an energetic component (HOMA = 1 – EN – GEO) so that the aromaticity is decreased by an increase of both the mean bond length (EN) and the bond alternation (GEO). Magnetic criteria are based either on the experimentally measured induced diamagnetic π-electron ring currents (via diamagnetic exaltation, molar diamagnetic susceptibility, and anisotropic polarizability), or on the calculated nucleus independent chemical shifts (NICS) (according to Schleyer) at a point situated in the ring center at distance zero from the molecular plane, NICS(0), or at a distance of 1 Å from that plane, NICS(1) [31].

A recent debate about the multidimensional character of aromaticity took place for several years between Katritzky and coworkers on one hand [32–34], and Schleyer [35–37] and Bird on the other hand [25]. Most of the aromatic systems discussed in this debate had either more than one heteroatom, or were five-membered. With a limited set of compounds investigated by Schleyer et al., it appeared that there is a satisfactory agreement between all these criteria, i.e., that aromaticity is unidimensional. However, the former group of authors extended the set, and found by means of principal component analysis that there are at least two orthogonal principal components, i.e., that aromaticity has a multidimensional character. This was acknowledged in a paper coauthored by the former group plus Bird [38]. Finally, a joint paper entitled "To what extent can aromaticity be defined uniquely?" was published in 2002 by Cyrañski et al. [39]. It stressed that aromaticity is not a directly measurable quantity and has no precise quantitative and generally

accepted definition, like many other important chemical concepts such as electronegativity or van der Waals radius. From the first two paragraphs of its conclusion, one has to cite ad-literam the following phrases [39]:

> We draw two general conclusions from the above data. On one hand: energetic, geometric, and magnetic indices of aromaticity all allow a rough division of conjugated cyclic compounds into three major groups: aromatic, nonaromatic, and antiaromatic. In this sense they contain similar information and show significant collinearity. Hence, various manifestations of aromaticity are related, at least to some extent and from a philosophical point of view aromaticity as an abstract idea can be regarded as a one-dimensional phenomenon.
>
> On the other hand: practically within any one of these three main groups, and in particular for the group of aromatic structures, which are of major practical importance to experimental chemists, the indices are not correlated. In practical applications energetic, geometric and magnetic descriptors of aromaticity (even if optimally chosen) do not speak with the same voice. Thus in this sense the phenomenon of aromaticity can be regarded essentially as being statistically multidimensional.

The multidimensional (and scale-dependent) character of aromaticity gives rise to a wide diversity of ways in which one may vary structural factors, such as ring size, electrical charge, number of condensed rings, etc. *In this chapter, the factor that will lie at the center of discussion will consist of varying the number of protons in the nucleus of only one of the ring atoms of benzene or, in other words, of replacing one CH group of benzene by a heteroatom*. Let it be said that even the replacement of a hydrogen atom in benzene by a substituent exerts a similar influence on chemical properties as the above-mentioned replacement by a heteroatom, as one may see in the nucleophilic substitutions of 4-chloronitrobenzene and 4-chloropyridine, or in the similar reactivity of pyrrole and phenol.

Because one of the most important changes associated with this virtual introduction of heteroatoms into aromatic hydrocarbons is connected with the different electrical charges of the atomic nuclei, including the shielding due to substituents attached to the heteroatom, it is expected that more electronegative atoms than carbon (such as oxygen and nitrogen) will decrease the π-electron density in the aromatic ring. On the other hand, atoms more electropositive than carbon (such as silicon or boron) will increase this π-electron density. However, one must also consider that marked changes are associated with bond distances and bond angles, or the fact that *d*-electrons may be involved for atoms with $Z > 20$, or that *d*-orbitals may participate even for silicon, phosphorus, or sulfur.

3 Nomenclature

We will use preferentially the current IUPAC nomenclature. On replacing a carbon atom in an aromatic hydrocarbon by a heteroatom, one can name the resulting system by combining the heteroatom's name (using the suffix "a" for the heteroatom) with the name of the hydrocarbon, e.g., pyridine may be called azabenzene. However, on replacing a heteroatom by another one, the new heteroatom's name

is combined with the former heterocycle name, but the suffix for the new heteroatom is "o" as in thiopyrylium or selenopyrylium. We shall not use the alternative names "thiinium" or thioniabenzene" for thiopyrylium. For brevity, along with IUPAC names such as 4*H*-pyran-4-one, we shall also use the shorter names such as 4-pyrone.

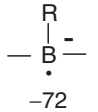
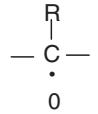
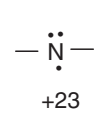
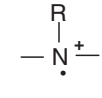
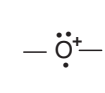
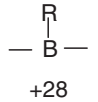
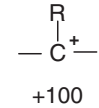
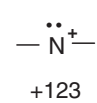
The names of groups in the periodic system are "halogens" for group 17, "chalcogens" for group 16, and "pnictogens" for group 15 (from the Greek words for salt, bronze, and to choke, respectively). The alternative spelling "pnicogens" cannot lead to derivations like "pnictides." Other groups will be denoted by their first element or by the number of that group, e.g., the carbon group for group 14, or the boron group for group 13. The periods for main group elements will be denoted by their numbers, namely period 1 with H and He; period 2 (or first-row) with Li through Ne; period 3 (or second row) with Na through Ar, etc.

4 Aromatic Six-Membered Rings with One Heteroatom

An early and ambitious project of this author had been to find all possible monocyclic aromatic systems by using graph–theoretical techniques, i.e., solutions of the "necklace problem" (enumerating all possible ways to assemble a necklace from a given number of beads having a given number of colors) [40]. The chemical counterpart was to find all isomers of rings formed from three types of sp^2-hybridized atoms having zero, one, or two *p*-electrons in the non-hybridized orbital (*Z*, *Y*, or *X*-type atoms, respectively). According to Pauli's principle, these three are all possible atom types forming an *m*-membered aromatic ring $X_xY_yZ_z$, when $x + y + z = m$, and $2x + y = 4n + 2$ according to the Hückel rule. Depending on the electronegativity of the substituent R connected to a heteroatom, the electronegativity (for R = H) relative to a CH group in benzene was assigned, as seen in Table 2. When R is different to H the relative electronegativity (or the "aromaticity constant" k_R) is approximated by $k_R = k_H + 20\sigma_{p-R}$, where σ_{p-R}, is the Hammett value for the *para*-R substituent. The "global electronegativity" of the ring is then $K = \Sigma_i K_i$ with the summation extending over all ring atoms. Arbitrarily, the global electronegativity for the tropylium cation (with six Y = CH and one Z = CH^+) was taken to be +100, and for the cyclopentadienide anion (with four Y = CH and one X = CH^-) to be −100. Practically all known stable aromatic systems have global electronegativities $-200 < K < +200$. For the purpose of the present discussion, one needs to consider only one Y-type heteroatom, along with five carbon atoms in the ring.

Of course, with atoms from lower periods of the periodic system, such as P or S, it is possible to have aromatic systems that are not simply homologs of pyridine or pyrylium, (i.e., phosphinine and thiopyrylium, respectively) but also systems with $P^{(V)}$ and $S^{(IV)}$, i.e. phosphabenzene (λ^5-phosphinine) and thiabenzene, respectively. However, in some cases the aromaticity is strongly perturbed, as for instance in selenabenzene derivatives stabilized by electron-withdrawing groups, when these compounds are shown to be zwitterionic.

Table 2 "Aromaticity constants" (relative electronegativities) of first-row atoms

X					
		–100	–77	–26	–3
Y						
	–72	–50	0	+23	+74	+97
Z						
	+28	+50	+100	+123		

In theory, with heteroatoms from lower periods, it should be possible to have even heteroaromatic systems with $I^{(III)}$ (iodabenzene), but so far no such compounds have been found in a literature search.

A collection of calculated NICS data for the usual main group elements is shown in Fig. 1 [41]. It reproduces in the upper row the Y-type elements from Table 2. The NICS(1) values correlate more faithfully with aromaticity than NICS(0) values [41]. According to these values, among rings with first-row atoms, neutral benzene derivatives have the highest NICS(1) data. For lower rows of the periodic system the highest values are for rings with one pnictogen atom (it will be seen later that, except for pyridine, quaternized cationic systems are not accessible for such rings).

Other features of monocyclic six-membered aromatic systems with one heteroatom are their geometries (bond lengths and bond angles), which are displayed in Fig. 2 [42, 43]. These are experimentally determined ground-state geometries obtained by microwave spectroscopy for pyridine, combined electron diffraction and microwave investigation for phosphinine, and X-ray crystallography for silabenzene and germabenzene bearing a bulky kinetically stabilizing 4-Tbt substituent, where Tbt is an abbreviation for 2,4,6-tris[bis(trimethylsilyl)methyl] phenyl. The data in Fig. 2 for the Tbt-substituted silabenzene and germabenzene have averaged values for the 2/6 and 3/5 bond angles in the ring (which differ by at most 0.3°), but the bond lengths for the 2–3 and 5–6 CH groups present more marked differences owing to the orientation of the 4-Tbt group.

It is known that anisole, 4-methoxypyridine, and its protonated congener have a ground-state conformation with the O–CH_3 bond eclipsed (coplanar with the aromatic ring). The torsional barriers are 3, 4.4, and 9 kcal mol^{-1}, respectively, in agreement with the increasing electronegativity of the heteroatom. An even lower barrier (less than 1 kcal mol^{-1}) is calculated for 4-trifluoromethoxypyridine. High-level ab-initio and density functional theory (DFT) calculations for a larger set of

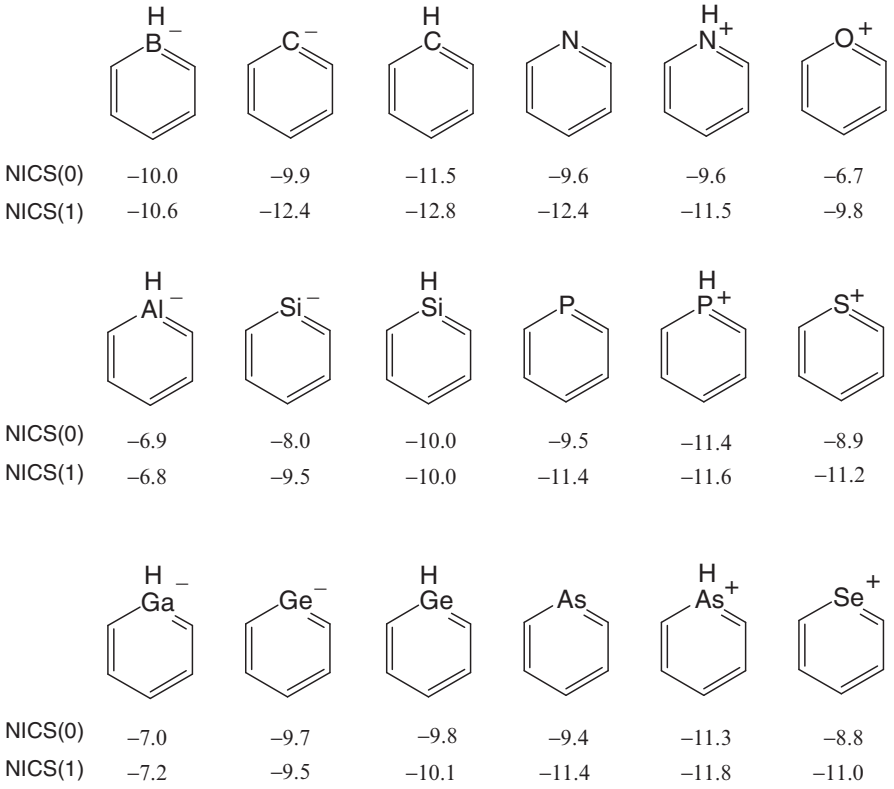


Fig. 1 NICS data of monocyclic six-membered aromatic systems with one heteroatom from groups 13–16 and periods 2–4, including cations and anions [41]

monocyclic six-membered aromatic systems with one heteroatom from groups14–15 and periods 2–4 devoid of electrical charges resulted in geometries that are very similar to those displayed in Fig. 2. In addition, rotational barriers have been calculated, resulting in values that are higher by about 1.5 kcal mol^{-1} for group 15 heteroarenes than for group 14 heteroarenes. Similarly, for methoxyarenes having electron-withdrawing groups (EWGs), one also obtains higher barriers, in agreement with the effect exerted by introducing electronegative heteroatoms. With increasing period numbers, the rotation barrier decreases, also in agreement with the decreasing electronegativity of the heteroatom [43, 44].

In Table 3 one can see experimental and calculated dipole moments for aromatic six-membered rings with one heteroatom [45]. Bond lengths increase and electronegativities decrease with increasing period numbers. With group 14 heteroatoms, the maximum dipole moment is attained for stannabenzene for the product of charges with distances. With group 15 heteroatoms, pyridine has the highest dipole moment as a result of the high electronegativity of nitrogen.

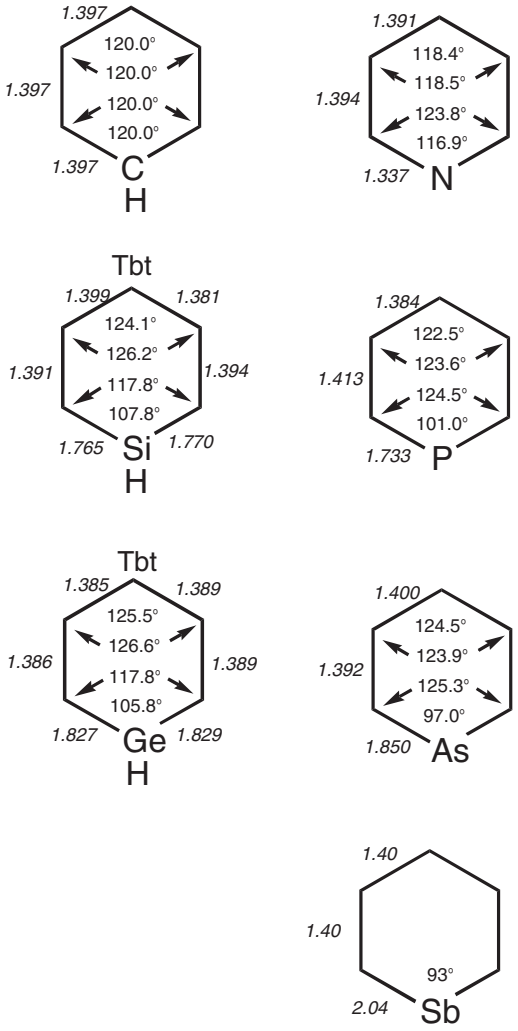


Fig. 2 Bond lengths (in Å, shown *outside* the rings) and bond angles (shown *inside* the rings) of monocyclic six-membered aromatic systems with one heteroatom from groups 14–15 and periods 2–4 devoid of electrical charges

Table 3 Dipole moments of valence-isoelectronic series of benzene [45]

Molecule	Formula	Dipole moment (D)	Data
Benzene	C_6H_6	0.000	
Silabenzene	C_5H_6Si	0.139	AM1
Germabenzene	C_5H_6Ge	0.916	AM1
Stannabenzene	C_5H_6Sn	1.505	PM3
Plumbabenzene	C_5H_6Pb	1.097	PM3
Pyridine	C_5H_5N	2.150	Exper.
Phosphabenzene	C_5H_5P	1.844	AM1
Arsabenzene	C_5H_5As	1.575	AM1
Stibabenzene	C_5H_5Sb	1.534	AM1
Bismabenzene	C_5H_5Bi	1.306	PM3

Semiempirical theoretical methods: AM1 = Austin model 1; PM3 = para-metrized model 3

In the following sections, a more detailed analysis of the aromaticity will be presented for various sets of six-membered rings with one heteroatom arranged according to the groups of the periodic system, from right to left. Since curricula of organic chemistry contain detailed information on benzene and pyridine, it will be assumed that only the less-known systems need information on their properties. We shall emphasize not only the physico-chemical properties or theoretical approaches for the determination of aromaticity, but also the chemical behavior, which is closer to a chemist's heart. Because of space limitations, synthetic methods will seldom be mentioned. Special attention will be paid to the extremes of electronegativity: pyrylium cations at the beginning (Sect. 5), and metallabenzenes at the end of the discussion (Sect. 11).

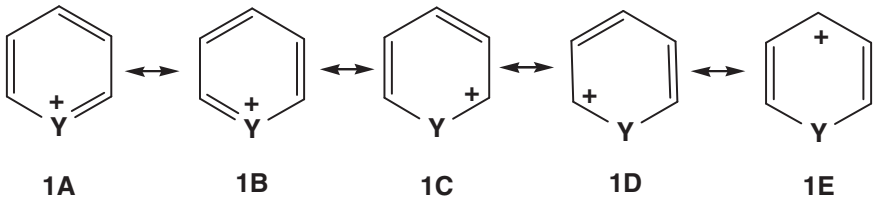
5 Pyrylium Cations

With oxygen as the most electronegative element that can be part of an aromatic ring replacing a CH group in benzene (Y-type atom according to Table 1), pyrylium cations are energetically close to acyclic compounds, so that they are easily formed from acyclic precursors and open easily their ring. Systematic surveys are available for syntheses and reactions of pyrylium salts [46–51]. Because of their ionic character, they can be easily separated in pure form from the non-polar starting materials. They are related to benzo[*b*]pyrylium cations, the colored plant constituents (anthocyanidins, chromylium, flavylium and xanthylium salts), to benzo[*c*]pyrylium or isobenzopyrylium cations, and to dibenzopyrylium (xanthylium) cations. An historically important moment for the development of the aromaticity concept was the proof that 4-pyrone is protonated and methylated at the exocyclic oxygen (and not at the ring oxygen like an oxonium salt) resulting in a pyrylium cation, leading to the idea that 4-pyrone may react as if it possessed two formulas [52]. When Baeyer reacted 4-pyrone with Grignard reagents obtaining, in 1911, the first pyrylium salts having alkyl substituents instead of hydroxy or alkoxy substituents, it was astonishing to see that such an oxonium salt could exist unchanged in water [53], but this was recognized as being due to aromaticity.

Among the uses of pyrylium salts (especially with aromatic substituents), one should mention their applications in the photographic and reprographic industries, photosensitizers in electrophotography, anticorrosion agents, fluorescent dyestuffs, luminescent paints, laser dyes, and especially as photoinduced electron-transfer agents for initiating polymerizations and photo-cross-linking [54–56]. Many patents have been issued for using pyrylium salts as photoconductor, photoimaging, and electro-photo-reprographic materials. Also, pyrylium salts are convenient intermediates for the manufacture of sterically hindered non-nucleophilic bases, as will be shown when discussing pyridines.

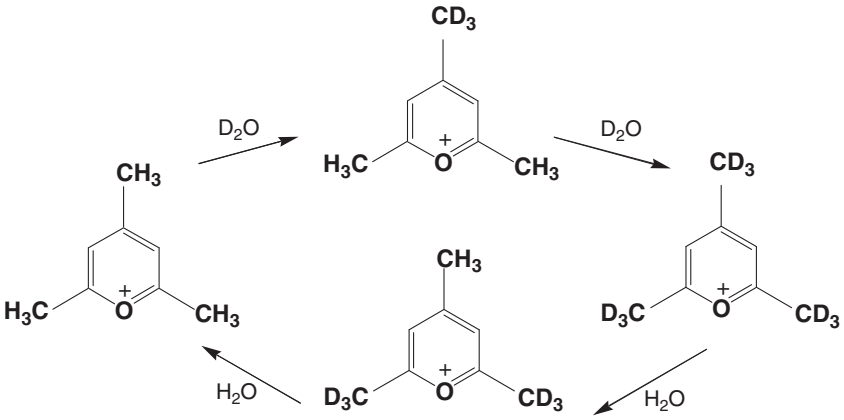
Like all six-membered rings with one heteroatom (Y) that is more electronegative than carbon, the electron distribution in pyrylium cations may be represented by resonance structures **1A**–**1E**. In pyrylium salts, the 2 and 6 positions

(α-positions) have the highest partial positive charge followed by the 4- or γ-position.



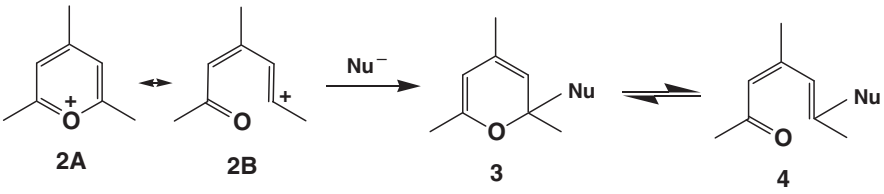
1A **1B** **1C** **1D** **1E**

As a consequence, benzylic protons in α- and γ-alkyl groups (but not in β-positions) are acidic and in water are in equilibrium with the corresponding methylenepyrans water at pH <5. Because the symmetric γ-methylenepyrans (γ-anhydrobases) are more stable than α-methylenepyrans [57], the isotopic exchange with deuterium oxide proceeds about ten times faster in γ than in α, and this allows the synthesis of regiospecifically deuterated alkylpyrylium salts, which can then be converted into other deuterated compounds because the reaction with nucleophiles takes place even faster [58, 59].

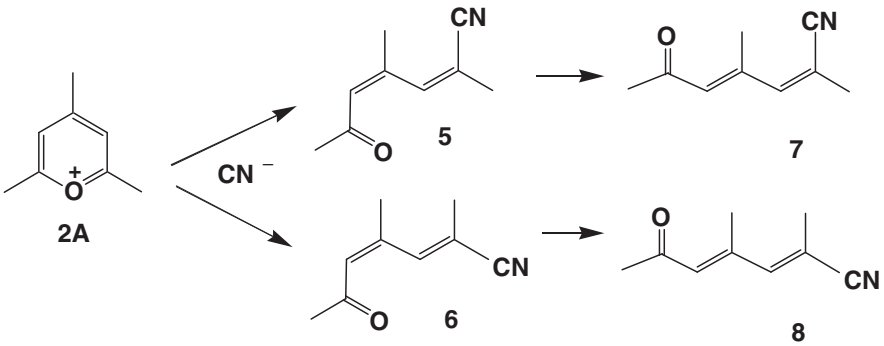


The addition of mild nucleophiles occurs preferentially in α (as described below) but with hydride, organomagnesium, or organolithium reagents addition in γ can also be observed, leading to isolable γ-pyrans.

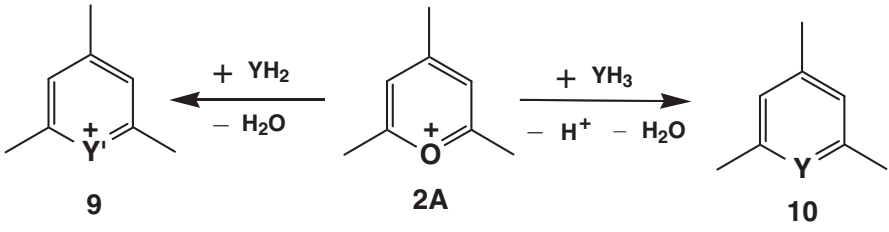
Usually, the α-pyranic addition products (**3**) cannot be isolated because they isomerize immediately in a thermally allowed electrocyclic process affording acyclic dienones (**4**), which in many cases react further. Therefore, pyrylium salts **2A** react with most nucleophiles as if they had the electronic structure **2B**, and thus the pyrylium cation behaves as a useful synthon, namely the last vinylog in the series of acyl halides (C_1 synthon) – β-halovinyl ketones (C_3 synthon) – pyrylium (C_5 synthon) [50, 51].



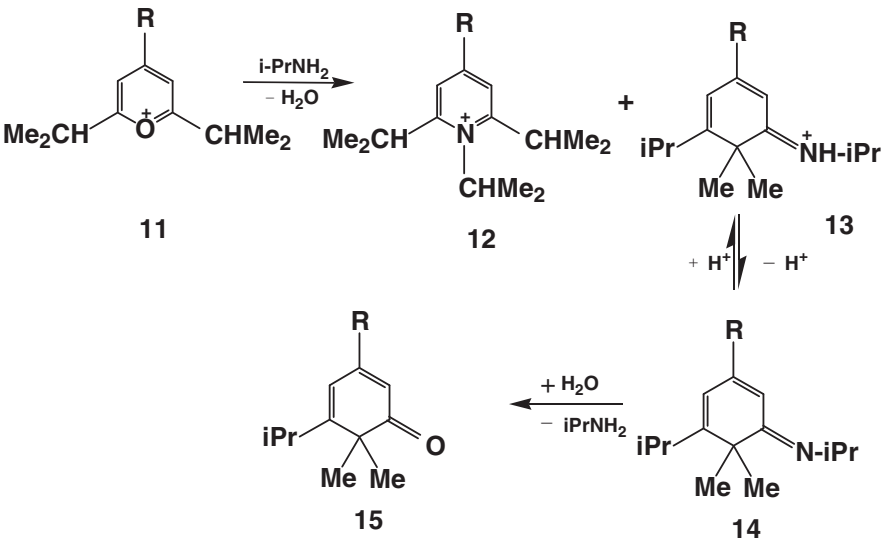
Only in a few cases are the acyclic dienones stable enough to afford isolable products. Thus on treating 2,4,6-trialkylpyrylium salts with aqueous alkali cyanides, a mixture of two diastereomeric 5-cyano-2,4-dienones resulted. When the alkyls are methyl groups, the two liquid isomers are 2-*Z*,4-*Z*, 2,4-dimethyl-6-oxo-2,4-heptadienonitrile (**5**, 95%) and the 2-*E*,4-*Z* isomer (**6**, 5%). On diluting their solutions in concentrated hydrochloric acid, the corresponding crystalline diastereomers (**7** and **8**) are formed [60, 61].



The usual course of treating pyrylium salts with nucleophiles that have hydrogen atoms at the nucleophilic center results in an ANRORC (attack by nucleophile, ring opening, ring closure) reaction. When the new ring-closed product is a six-membered ring with one heteroatom, the new heteroatom is, of course, less electronegative than oxygen, so that the reaction is enthalpy-driven. Except for converting pyrylium cations into metallabenzenes or borabenzene anions, practically all other heterocycles discussed in this article (cations **9** or neutral systems **10)** can be obtained from pyrylium salts, e.g., hydrogen sulfide → thiopyrylium cations (Y′ = S); primary amines → pyridinium cations (Y′ = NR); ammonia → pyridines (Y = N); phosphines → phosphinins (Y = P) [47].

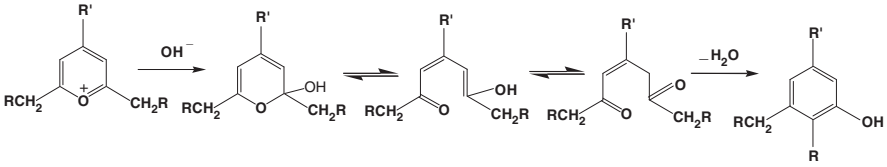


However, when steric factors are involved, along with the aromatic pyridinium salt **12**, formed from 2,6-diisopopyl-4-alkylpyrylium salts and isopropylamine, one also obtains an unexpected cyclohexadienylidene-iminium salt **13**, which can be deprotonated to the corresponding imine **14**. This can then be hydrolyzed affording the non-aromatic cyclohexadienone **15**. The two reaction products **12** and **13** are derived from the same intermediate by intramolecular dehydration, incorporating into the ring a nitrogen atom for the former product, whereas the latter product is obtained by incorporating the central isopropyl carbon atom [62, 63].



With hydroxide anions (or with water at pH >5) pyrylium salts form pseudobases **16** (2-hydroxy-2*H*-pyrans) that tautomerize to acyclic 3-penten-1,5-diones **17** via a thermally allowed electrocyclic reaction. Most ring transformation reactions of pyrylium salts involve a similar ring-opening.

With carbon-centered nucleophiles such as acetonitrile, nitrobenzene, or β-ketoesters (e.g., ethyl acetoacetate), one replaces the oxygen heteroatom by a carbon atom forming benzonitrile, nitrobenzene, and acetophenone derivatives, respectively [64]. With diethyl malonate, the benzene derivatives that result contain two of the malonate carbon atoms [65]. With hot alkali hydroxides, the pseudobases of pyrylium salts with α-methyl or α-methylene groups undergo an interesting intramolecular dehydration of the resulting ring-opened tautomeric pseudobase, resulting in phenols **18** that incorporate the α-methyl(ene) group into the benzene ring.



Many other reactions of pyrylium salts have been described, converting this readily accessible conjugated C_5-synthon into monocyclic aromatic systems with five-membered rings (2-acylfurans, isoxazoles, pyrazoles), or aromatic bicyclic systems (naphthalenes, indolizines),

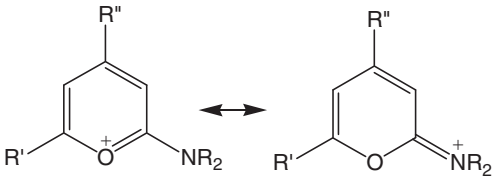
In addition to this chemical behavior that shows how easily pyrylium salts undergo ring-opening reactions, all energetic, geometric, and magnetic criteria indicate that pyrylium salts are less aromatic than most of the other six-membered rings with one heteroatom because the high electronegativity of the oxygen tends to retain π-electrons. However, it is undeniable that the unsubstituted pyrylium cation is stable in sufficiently acidic aqueous solutions, or in pure acetic acid (from which the perchlorate can be recrystallized). This behavior makes it quite different from trialkyloxonium salts (which are immediately hydrolyzed by water) and is due to aromaticity.

All physical properties of pyrylium salts (unsubstituted or substituted with alkyl and/or aryl groups) prove the aromaticity of these cations: vibrational spectra [66], mass-spectral fragmentations [67], magnetic properties [68–70], and electronic absorption spectra [71]. It should be mentioned that there is a close similarity between the electronic absorption bands of pyrylium salts and those of benzene, easily recognized by the marked bathochromic effect of substituents in γ-position of pyrylium salts on one of these bands. Two-photon absorption spectra of 2,4,6-triarylpyrylium cations [72] may be used in optical data storage, lasing, and photodynamic therapy.

A word of caution is needed when discussing perchlorates: the unsubstituted pyrylium perchlorate like tropylium perchlorate is readily explosive; it should be handled with utmost care, and in very small amounts. On the other hand, 2,4,6-trisubstituted pyrylium perchlorates (“tertiary carbocations”) are less sensitive, but still need to be treated carefully. Tetrafluoroborates, triflates, or hexafluorophosphates are preferable. An interesting behavior of salts of organic cations having highly polarizable anions (iodide, sulfocyanate, selenocyanate, tetracyanopropenide) is the formation of colored charge-transfer complexes [73, 74]. Azide anions behave differently with variously substituted pyrylium salts, yielding ionic charge-transfer complexes or covalent adducts, depending on the temperature and steric factors [75].

On the other hand, pyrylium salts with secondary amino groups as substituents (**19A**) have a large contribution of vinamidinium resonance structures (**19B**), especially

when they have two such groups (e.g., when R″ = NR_2). In such cases, the rotation around the C–N bonds is restricted and the structure is trimethine–cyaninic, allowing electrophilic substitution of the methinic β-hydrogen. This type of electrophilic substitution is unprecedented for pyrylium salts, which usually react only by nucleophilic addition [76–78].



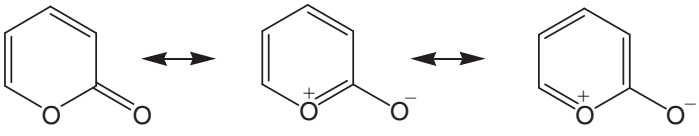
19A **19B**

By determining the bond lengths in 2,4,6-triphenylpyrylium salts with various substituents at the *para* position of the 4-phenyl ring, Krygowski and coworkers found a practically linear dependence between the HOMA index and the Hammett σ_p parameter, indicating for amino substituents a considerable bond localization (with corresponding decrease of HOMA) [79–81].

Quantum-chemical calculations for pyrylium including one, two, or three water molecules using DFT and 6–31 + G(d,p) basis set revealed that the aromaticity (estimated by harmonic oscillator stabilization energy, HOSE; natural resonance theory, NRT; harmonic oscillator model of aromaticity, HOMA; and nucleus-independent chemical shifts, NICS) is not influenced by water molecules [82].

For 3-pyrylium oxides, the *Science of Synthesis (Houben–Weyl)* series has dedicated a separate chapter [83]. Substituted pyrylium-3-oxides are zwitterionic compounds and participate in intra- or intermolecular [3 + 2]-cycloadditions with alkenic double bonds, or dimerize by [3 + 3] cycloadditions.

Much more stable are the 2- or 4-oxides, i.e., α-pyrones (unsaturated lactones) **20** and γ-pyrones, which could, in principle, have aromatic character owing to their zwitterionic resonance structures (**20A**–**20C**). However, although protonated pyrones are definitely aromatic, the neutral compounds appear to have very little aromaticity. Bird's aromaticity index I_6 for pyrylium is only 65.8% in comparison with benzene, whereas for 4-pyrone it is 37.2% and for 2-pyrone it is only 32.9%, as seen in Table 4 [22]. In agreement with Table 2, the ring O–(C = O) bond in **20A** is a type X–Z bond, whereas the ring $O^+ = (C–O^-)$ bond in the two other resonance formulas is a Y–Y bond.



20A **20B** **20C**

Table 4 Bird's aromaticity index for six-membered heterocycles with one heteroatom

Aromatic six-membered ring	Bird index I_6
Benzene	100.0
Pyrylium cation	65.8
Pyran-2-one	32.9
Pyran-4-one	37.2
Pyran-4-thione	47.9
Pyridine	85.7
Pyridinium methiodide	66.7
Pyridinium dicyanomethylide	70.1
Pyridine *N*-oxide	74.4
4-Dimethylamino-pyridine *N*-oxide	73.6
4-Cyano-pyridine *N*-oxide	71.6
4-Nitro-pyridine *N*-oxide	67.4
3-Methyl-4-nitro-pyridine *N*-oxide	70.8
2-Hydroxymethyl-pyridine *N*-oxide	72.2
2,6-Dicarboxy-pyridine *N*-oxide	67.9
2-(*ortho*-Hydroxyphenyl)- pyridine *N*-oxide	62.0
Pyridinium *N*-nitroimine	76.0
Phosphorin	74.1
Arsenin	66.9

6 Other Chalcogenopyrylium (Thio-, Seleno-, and Telluropyrylium) Cations and Their Corresponding Chalcogenabenzenes

Owing to the gradually decreasing electronegativity of S, Se, and Te relative to oxygen, the chemical reactivity of the corresponding chalcogenopyrylium towards nucleophiles is lower than for pyrylium cations with similar substitution patterns. At the same time, the progressively higher covalent radii and increasing stability of higher oxidation states of these atoms makes such chalcogenopyrylium cations less stable towards oxidants. The fact that all such elements E may also involve their *d*-orbitals allows in principle the existence of higher oxidation states than E^{II} (this is the only possibility for the first chalcogen atom, oxygen), namely E^{IV} and E^{VI}, which could give rise to the corresponding λ^2- and λ^4-chalcogenabenzenes.

Several reviews on thiopyrylium salts are available, in addition to the literature data from *Comprehensive Heterocyclic Chemistry* [84, 85]: specifically for thiopyrylium [86, 87], or together with other chalcogenopyrylium cations [88]. For selenopyrylium, two reviews have appeared [89, 90], and for telluropyrylium a review that also encompasses biomedical applications [91]. Among the uses of thiopyrylium salts [88, 92], one can cite applications such as photographic materials, laser techniques, infrared-absorbing dyes, electron-transfer photosensitizers, photoinitiators in holographic recorders, electrophotographic photoreceptors, and photoconductive polymers for solar cells. Biomedical applications include the antitumor agent AA1

[2,6-bis-(4-aminophenyl)-4-(4-dimethylaminophenyl)-thiopyrylium chloride] and various other salts for photodynamic therapy [91–94].

As expected on the basis of the higher stability of sulfonium salts as compared with oxonium salts, thiopyrylium cations are more stable and less reactive than pyrylium cations: hydride-accepting ability decreases in the order pyrylium > selenopyrylium > thiopyrylium [95]. 2,4,6-Triphenyl-thiopyrylium salts react with ammonia and primary alkylamines forming the corresponding pyridine and pyridinium salts, respectively, but they do not react with aniline or its derivatives [96–99]. As described below, the Se- or Te-analogs are less stable than the thiopyrylium salts.

Catalytic reduction of thiopyrylium salts under forcing conditions yields tetrahydrothiopyrans, but oxidation with manganese dioxide of the unsubstituted thiopyrylium cation (first obtained by Pettit [100]) affords thiophene-2-carbaldehyde in a reaction without analogy to pyrylium salts [101]. Like α- and γ-benzylic positions in pyrylium salts, methyl(ene) groups of alkyl substituents in thiopyrylium cations are usefully acidic and as such the corresponding anhydrobases may be trapped by various nucleophiles.

Physical properties of thiopyrylium salts reflect their aromaticity [94]. The ring is planar. Electronic absorption bands appear at longer wavelengths than for pyrylium or pyridinium cations with the same substitution pattern. According to the relative anisotropies in NMR spectra, the aromaticity ordering of six-membered heterocycles with one heteroatom is: $CH > S^+ > N \approx P > SiH \approx O^+$ [102]. This means that among all chalcogenopyrylium cations, thiopyrylium is the most aromatic because it has a heteroatom that has exactly the same Pauling electronegativity as carbon, and a covalent radius only slightly higher than that of carbon. There is an ongoing discussion about whether *d*-orbitals are involved in thiopyrylium, and both affirmative and negative opinions have been advocated, but apparently there is no big difference between the results.

The NMR chemical shifts of chalcogenopyrylium salts indicate the presence of ring currents, but the values also reflect the anisotropy of the heteroatom, which increases with its atomic number. Radics and coworkers determined homo- and heteronuclear coupling constants [103–105], and the results are presented in Table 4. We shall discuss pyridine and pyridinium derivatives later, but now one may observe that for the chalcogenopyrylium cations there is a monotonous decrease of the ^3J(C-2, H-6) values with decreasing electronegativity of the heteroatom. Homonuclear C–C and H–H coupling constants do not vary regularly but one may observe that pyrylium has extreme values in comparison with the two other chalcogenopyrylium salts (Table 5). This is undoubtedly due to its lower aromaticity, caused by the fact that its oxygen heteroatom has the highest possible single perturbation of the ring current due to its extreme electronegativity.

The fact that pyrylium salts easily form anhydrobases in water over a large range of pH values, and pseudobases at pH >5, makes such salts incompatible with biomedical applications, but the highly fluorescent 2,4,6-triarylpyrylium salts with phenyl or *para*-anisyl groups have various applications in reprographic industries. On the other hand, chalcogenopyrylium cations with other atoms (S, Se, Te) are less

Table 5 NMR coupling constants (Hz) in $D_3C–CN$

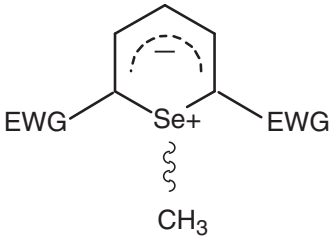
J	Pyrylium	Thiopyrylium	Selenopyrylium	Pyridine	Pyridinium	Pyridine-*N*-oxide
$^{2}J(^{15}N, H\text{-}2)$				−10.93	−3.01	+0.47
$^{1}J(^{15}N, C\text{-}2)$				+0.62	−11.85	−15.24
^{4}J(H-2, H-6)	0.40	3.45	3.08	−0.15	+1.00	+1.89
^{3}J(H-2, H-3)	4.21	8.73	8.95			
^{4}J(H-2, H-4)	1.84	1.06	1.12			
^{5}J(H-2, H-5)	1.00	0.89	0.95			
^{3}J(C-2, H-6)	6.31	5.95	4.58	+11.16	+6.32	+4.10
^{1}J(C-2, C-3)	59.5	56.5	56.7	54.2	59.1	
^{1}J(C-3, C-4)	50.4	54.3	55.4	53.7	52.1	
^{3}J(C-2, C-5)	9.4	9.8	9.3	14.0	9.1	

prone to ring opening, and may be used as photoactivated single-electron transfer agents for a variety of technological and biomedical uses, the main one being possible application as anticancer agents [92–94].

Among the numerous theoretical calculations of thiopyrylium cations, Palmer's papers [106–109] and three earlier reports will be mentioned [110–112]. The last one includes also sulfur analogs of 4-pyrones, which may involve either the endo- or the exocyclic oxygen atom, or both. The calculated electronic structure indicates the following aromaticity order based on the lowest π-orbitals: thiopyran-4-thione > thiopyran-4-one > pyran-4-thione > pyran-4-one [113]. An interesting photochemical ring-opening reaction was reported for thio-analogs of 2-pyrone (thiopyran-2-one and pyran-2-thione), resulting in the interconversion of these two compounds [114]. In addition, when considering 2-pyrones and ring- or imino-nitrogen heteroatoms, a fairly complicated picture emerges [115].

After having examined the clear-cut aromaticity of chalcogenopyrylium salts, one must mention that the situation is quite different for thiabenzene when the higher oxidation state of sulfur (S^{IV}) must be taken into account. In this case, the valence-shell expansion of sulfur leads to a non-planar zwitterionic system. In the 1960s, Price and coworkers claimed to have synthesized thiabenzene derivatives from thiopyrylium salts and organolithium derivatives [116–119], but soon afterwards Mislow and coworkers found that the products were oligomeric materials of undetermined structure [120–124]. By means of careful experiments with various thiabenzene precursors in NMR tubes, it was found that the thiabenzene structure was actually a cyclic sulfur-ylide. Strangely, some of the ex-coworkers of Price have continued to publish recent theoretical data about Price's "thiabenzenes" [125] without referring to the data of Mislow et al. True λ^4-thiabenzenes possessing fair stability when substituted by electron-withdrawing substituents (EWG = carbalkoxy, cyano, benzoyl) were, however, prepared by Hori [126–130], another ex-coworker of Price. The ylidic properties of λ^4-thiabenzenes were established by spectral and chemical evidence. Their thermal decomposition affords alkyl-rearranged thiopyran products, and (from benzoyl-substituted thiabenzenes) ring-contracted thienofurans and thiophenes. A different synthetic

strategy was employed by Weber et al., who stabilized thiabenzenes and thiabenzene 1-oxides as ligands of metal complexes [131–133]. True selenabenzene derivatives **21** can also be prepared when they have two EWG groups in α-positions [90, 134].



21

The molecular structure of the 2,6-dibenzoyl-selenabenzene derivative was determined by X-ray diffractometry and NMR analysis. The molecule is bent along a line between C-2 and C-6, with a dihedral angle of 5°, so that the structure is zwitterionic, with the negative charge delocalized on the two EWG groups. Two stereoisomers exist (wavy line in **21**). The bond lengths for the C_5-fragment denote electronic delocalization (dotted line). The two C–Se bond lengths (1.915 and 1.918 Å) agree with C(sp^2)–Se, and the H_3C–Se (1.98 Å) is a C(sp^3)–Se bond; a C = Se bond would have a length of only 1.67 Å. The chemical behavior of selenabenzenes denotes lack of aromaticity: refluxing in benzene for 2.5 h leads to rearrangement of the methyl group, which becomes linked to C-2 or C-4 affording a mixture of 2*H*- and 4*H*-selenopyrans. The purple solution of the selenabenzene in chloroform becomes colorless in a week on exposure to air. The products in methanol are a selenopyran-4-one and a 1,4-pentadien-3-one.

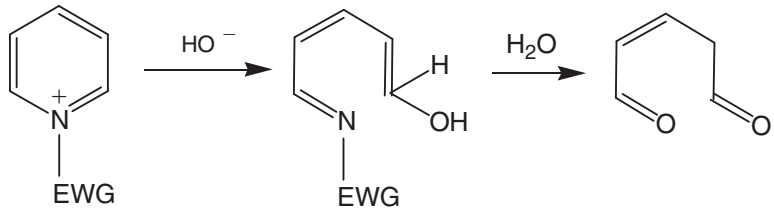
7 Pyridinium Cations and Pyridine

We assume that readers are familiar with facts concerning the similarities and differences between benzene and pyridine derivatives. Pyridine is a base (pK_a = 5.19, affording a pH of 8.5 for a 20% aqueous solution. It has a dipole moment of 2.15 D, as seen in Table 3). The fact that the nitrogen heteroatom with a higher electronegativity than carbon causes a depletion of π-electrons in γ and in α positions leads to regioselective electrophilic substitution in β positions and, conversely, facilitates nucleophilic attack mainly in α positions, e.g., affording α-picoline and lithium hydride from the reaction of pyridine with methyllithium.

Steric shielding of the heteroatom in pyridine results in non-nucleophilic bases such as 2,6-di-*tert*-butylpyridine and its 4-methyl congener (the latter is easily

accessible from the corresponding pyrylium salt, obtained by the Balaban–Nenitzescu–Praill method by dipivaloylation of isobutene) [135]. A different type of such a non-nucleophilic base is 2,6-diisopropyl-3,5-dimethyl-4-ethylpyridine, resulting from a similar diacylation using triethylcarbinol as the source of the alkene; a double Janus effect is responsible for the orientation of the α-isopropyl groups such as to mimic *tert*-butyl groups [136].

On protonating or quaternizing pyridine to a pyridinium salt, the above chemical features of π-electron deficiency become more marked. In addition, a new reaction becomes possible, namely ring opening, due to the higher electronegativity of the heteroatom plus the EWG connected to the heteroatom. This happens with EWG = cyano (von Braun reaction), 2,4-dinitrochlorobenzene (Zincke reaction), 4-pyridyl, or *N*,*N*-dimethylcarbamoyl [137, 138]. The best synthesis of the sodium salt of glutacon-dialdehyde **23** consists in preparing the zwitterionic pyridinium salt **22** with EWG = SO_3^- followed by treatment with methanolic sodium methoxide. A close parallel with ring-opening reactions of pyrylium or chalcogenopyrylium salts can be made.



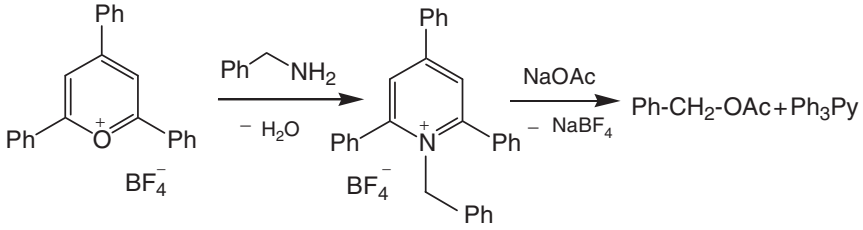
22 **23**

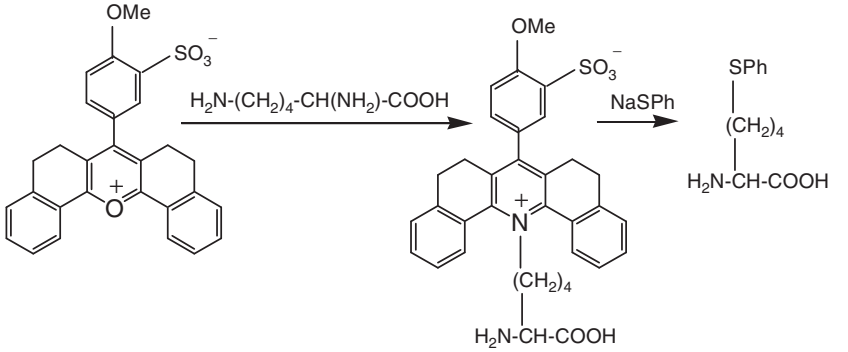
Alkyl-substituted pyridinium salts also exchange benzylic hydrogens with deuterated solvents with reversed regioselectivity in comparison with pyrylium salts because their γ-anhydrobases are less stable than α-anhydrobases [57].

"Green chemistry" makes increasing use of ionic liquids. Next to imidazolium salts, some pyridinium salts have also gained acceptance because when linear N-alkyl substituents are present, salts with tetrafluoroborate, hexafluorophosphate or a few other anions have melting points around or below room temperature. An interesting application of pyridinium salts with two hydrophobic substituents (long alkyl groups) is that such cationic lipids may be used as gene transfer agents [139 and literature cited therein].

An interesting reaction of pyridinium cations had its starting point in an observation made by Susan and Balaban [140]: 1-aryl-2,4,6-triphenylpyrylium salts (where the N-aryl groups have electron-donating *para*-substituents) easily underwent a C–C bond splitting with mild nucleophiles, forming 2,4,6-triphenylpyridine. Thus, on recrystallizing from ethanol 1-(4-methoxybenzyl)-2,4,6-triphenylpyrylium perchlorate, the products were 4-methoxybenzyl ethyl ether and 2,4,6-triphenylpyridine. Similarly, on heating *N*-methyl-2,4,6-triphenylpyrylium halides one obtains methyl halides and 2,4,6-triphenylpyridine. This observation was developed by Katritzky and coworkers into a new method for

replacing the amino group of primary amines by various nucleophiles. Using the intermediacy of pyrylium salts having sterically significant environments, the primary amine is first converted in high yield into a pyridinium salt, and then this salt is treated with the nucleophile, when the pyridine splits off as the leaving group. This alternative to the usual nucleophilic substitution of alkyl halides, tosylates, or triflates presents several advantages. Several reviews of this Katritzky reaction are available [141, 142].

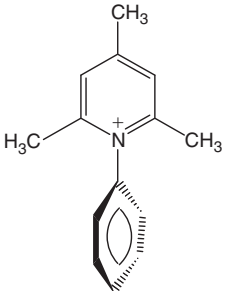




An interesting application of pyridinium salts is for the direct experimental determination of ring currents in a ring R: starting from the corresponding primary amine R–NH_2 and a 2,4,6-trimethylpyrylium salt, an N-substituted pyridinium salt is obtained. The two rings are practically orthogonal (for *N*-phenyl-2,4,6-trimethylpyrylium the dihedral angle determined by X-ray diffractometry is 85°) and whenever there are *ortho*-substituents on the R group, perfect orthogonality is ensured [143]. The ^{1}H-NMR chemical shift (ppm) for the two α-methyl groups appears at lower field than the γ-methyl when R is an alkyl or non-aromatic group. However, when R is aromatic, the α-methyl protons are shielded owing to the ring current, as seen in Table 6 [144, 145]. The difference *D* is a measure of the ring current for monocyclic rings of the same size. When *ortho*-substituents are present, when rings R are of different sizes or when R is polycyclic (naphthyl or anthryl), one must make corrections. On comparing thus phenyl with pyridyl rings it can be seen that pyridine has a slightly smaller ring current than benzene, whereas isoxazole has a very low ring current.

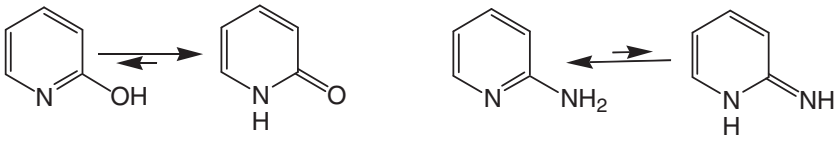
Table 6 Chemical shifts for 1-R-2,4,6-trimethylpyridinium salts in trifluoroacetic acid and the difference (*D*) between shifts for the α- and γ-methyl groups [144, 145]

Group R	α-Me_2 (ppm)	γ-Me (ppm)	*D* (ppb)
Methyl	2.82	2.58	−240
Phenyl	2.48	2.73	250
4-Tolyl	2.41	2.64	230
3-Tolyl	2.5	2.73	230
2-Tolyl	2.43	2.75	320
1-Naphthyl	2.43	2.86	430
2-Naphthyl	2.54	2.78	240
1-Anthryl	2.40	2.80	400
2-Anthryl	2.55	2.73	180
9-Anthryl	2.29	2.97	680
2-Pyridyl	2.56	2.80	240
3-Pyridyl	2.53	2.76	230
5-Methylisoxazol-3-yl	2.74	2.62	−80
Thiazol-2-yl	2.61	2.78	170



The tautomerism of 2-pyridones **25** that are favored over 2-hydroxypyridines **24** (and conversely, 2-aminopyridines **26** that are favored over 2-imino-derivatives **27**) plays a central role in the chemistry and biochemistry of all azines [146–148]. A comparison between *N*-methyl-2-pyridone and 2-methoxypyridine shows that the magnetic susceptibility of the former is about 20% greater than that of the latter [149].

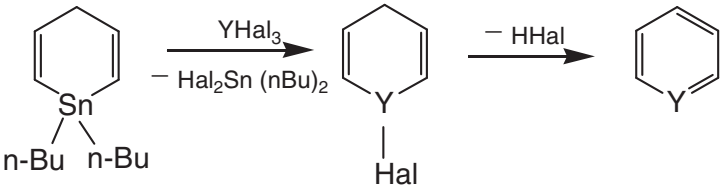
The Crick–Watson base pairing with the complementarity C–G and A–T (for DNA) or A–U (for RNA) is a consequence of the delicate balance between aromatic resonance energies and bond energies for CC, CO and CN single and double bonds.



24 **25** **26** **27**

8 Other Pnictogenabenzenes: Phosphabenzene (λ^3-Phosphinine and Congeneric λ^5-Phosphinines), Arsa-, Stiba-, Bismabenzenes

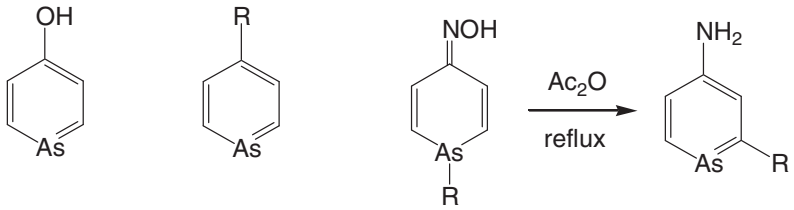
In this section we shall use interchangingly the names phosphabenzene and λ^3-phosphinine. Although pyridine has been known for more than a century, the first breakthrough for related heterocycles with other pnictogens occurred only in 1966 when Märkl (University of Regensburg, Germany) prepared 2,4,6-triphenyl-phosphabenzene from 2,4,6-triphenylpyrylium salts and phosphine [150]. Higher yields were obtained on replacing PH_3 by $P(CH_2OH)_3$ or $P(SiMe_3)_3$. 2,4,6-Triphenyl-phosphabenzene forms yellow crystals that are relatively stable to air, and presents X-ray diffraction spectra that unambiguously prove their aromaticity. It was therefore evident that (3*p*–2*p*) π-bonds can give rise to aromatic systems, and soon other authors (Dimroth [151, 152], Bickelhaupt [153–157], and Jutzi [158–160]) provided additional evidence for substituted and/or polycyclic congeneric systems. Then, Ashe III (University of Michigan at Ann Arbor, USA) using a method based on tin derivatives (**28**→**29**→**30**) [161, 162], succeeded in synthesizing unsubstituted pnictogenabenzenes with Y = P and As (which proved to be distillable liquids, somewhat air-sensitive, but stable to hydrolysis and to mild acids and bases). Stibabenzene is stable below −70 °C, and bismabenzene has a fleeting existence (proved spectroscopically and via chemical trapping) before it dimerizes. The strength of (*np*–2*p*) π-bonds with $n > 2$ decreases with increasing n, but it is still substantial for $n < 6$. Several reviews on their results were published by Märkl [163, 164] and by Ashe [165, 166]. Both Märkl [167–188] and Ashe [189–213] published dozens of papers about pnictogenabenzenes, but only a few of their papers will be cited here.



28 **29** **30**

An interesting aspect of these heterobenzenes is the closer similarity between benzene and arsabenzene than between benzene and pyridine or phosphabenzene, possibly due to the combined effects of electronegativity, covalent radius, and bond energy (nitrogen with higher electronegativity than carbon, and phosphorus with a very high P–O bond energy). Thus, arsaphenol (**31**) has $pK_a = 8.8$, close to the pK_a of phenol (9.9), smells like phenol, and does not tautomerize to a carbonyl derivative as does the pyridine congener. The colorless crystalline arsabenzoic acid (**32**, R = COOH) has $pK_a = 4.1$ similarly to benzoic acid ($pK_a = 4.2$). Arsabenzaldehyde (**32**, R = CHO) smells like almonds, and the ethyl ester (**32**, R = COOEt) has the same fruity aroma as ethyl benzoate (remember by contrast the nauseating odor of

cacodyl $Me_2As–O–AsMe_2$!). Arsa-aniline **34** can be obtained be rearrangement and aromatization from an arsa-cyclohexadienone-oxime **33** [214].



31 **32** **33** **34**

The molecular structure of 2,6-dimethyl-4-phenyl-λ^3-phosphinine shows full planarity of the heterocyclic ring, and a dihedral angle of 148.1° between the two rings; the C–P–C bond angle (102.9°) is about 4° larger than in tertiary phosphanes. Bond lengths (in Ångstrom) are shown in Fig. 2 on the outside of rings, and bond angles on the inside. Whereas pyridine has an almost regular hexagon, pnictogena-heteroaromatics have longer C–Y bond lengths and more acute C–P–C bond angles, but the planarity of the ring is conserved [165].

The NMR spectra provide, like the X-ray data, strong evidence for the aromaticity of pnictogena-hetarenes (group 15 heterobenzenes). In Table 7 one can see values of chemical shifts for ^{1}H-NMR and ^{13}C-NMR and (in brackets) coupling constants ^1J ^{13}CH. The spectacular gradual increase of chemical shifts for the 2- and 6-hydrogen atoms for heavier heteroatoms is due not only to the diatropic ring current, but also to the magnetic anisotropy of the heteroatom. After correction for this effect, residual downfield shifts relatively to benzene (δ_0 = 7.37 ppm) are observed (δ_0 = 7.0 ppm for phosphabenzene, 6.8 ppm for arsabenzene, and 6.6 ppm for stibabenzene), indicating decreasing aromaticity in this order. The ^{13}C-NMR data show little variation relative to benzene, except for the 2- and 6-carbon atoms, whose progressively higher downfield chemical shifts parallel those of the proton NMR, but with less well-understood causes. The similarity of ^1J ^{13}CH chemical shifts with those of benzene indicates sp^2 hybridization throughout the series.

The UV photoelectron spectra of the unsubstituted pnictogena-hetarenes allowed an almost perfectly linear correlation between the ionization energies $I_v(b_1\pi)$ of the

Table 7 NMR data for pnictogena-hetarenes: chemical shifts (δ in ppm) with coupling constants (^1J ^{13}CH in Hz) in brackets

Atom	C_6H_6	C_6H_5N	C_6H_5P	C_6H_5As	C_6H_5Sb	C_6H_5Bi
H-α	7.37	8.29	8.61	9.68	10.94	13.25
H-β	7.37	7.38	7.72	7.83	8.24	9.8
H-γ	7.37	7.75	7.38	7.52	7.78	7.8
C-α	128.7 (159)		154.1 (157)	167.7 (159)	178.3 (158)	
C-β	128.7 (159)		133.6 (156)	133.2 (157)	134.4 (153)	
C-γ	128.7 (159)		128.8 (161)	128.2 (161)	127.4	

molecules C_5H_5Y (Y = Bi, Sb, As, P, CH, and N) versus the atomic ionization energies *I*(E) of the free atoms. The slope of the straight line is 0.36, in excellent accord with the expected value ($0.33 = c_{Eb1}^2$) from the first-order perturbation of the benzene HMO orbital [189].

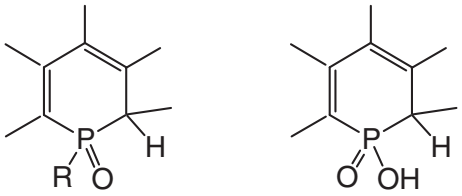
After having measured gas-phase dipole moments of pyridine and its P- and As-congeners [190], Ashe and coworkers checked the magnitude and direction of solution dipole moments by measuring them also for the 4-methyl-derivatives. In agreement with theoretical predictions, it was found [191] that all these three heterobenzenes have the same direction of dipole moments, although nitrogen has a higher electronegativity than carbon, but phosphorus and arsenic a lower electronegativity. The values of the solution dipole moments for C_5H_5N, C_5H_5P and C_5H_5As are 2.02, 1.46, and 1.02 D, respectively, whereas for the 4-methyl-derivatives the values are 2.57, 1.77, and 1.50 D, respectively.

The close aromaticity values for λ^3-phosphinine, pyridine, and benzene according to spectral, structural, theoretical, and energetic criteria are discussed in detail in Nyulászi's review [214].

The chemical behavior of this interesting family of heterobenzenes has both similarities and differences from pyridine. The most interesting aspect is that owing to the reduced electronegativity, electrophilic substitutions of arsabenzene take place with α, γ-regioselectivity instead of β-regioselectivity as in pyridine, provided that the electrophile does not increase the oxidation degree of the heteroatom. Indeed, nitration with acetyl nitrate affords 4-nitro-arsabenzene. Acylation with acetyl chloride or benzoyl chloride yields a mixture of α- and γ-acyl derivatives, and deuteration with $F_3C–COOD$ results in 2,4,6-trideutero-arsabenzene [204]. 4-Methyl-arsabenzene is acetylated by AcCl in CH_2Cl_2 in the presence of $AlCl_3$ affording 2-acetyl-4-methyl-arsabenzene. Qualitatively, arsabenzene is even more reactive in electrophilic substitutions than benzene [204].

The chemistry of phosphabenzene and arsabenzene is more similar to that of benzene than to pyridine in the complexation with metal derivatives. Indeed, whereas pyridine (a strong *n*-donor) forms σ-complexes with metal pentacarbonyls of Cr, Mo, and W (such complexes, involving the lone pair of the heteroatom, are also available from phosphabenzene and arsabenzene), the weaker *n*-donor character of phosphabenzene and arsabenzene favors π-complexes when using $M(CO)_3(MeCN)_3$. The π-complex with stibabenzene is more stable than the original heterobenzene. A sandwich complex was obtained from 2,4,6-triphenylphosphine and manganese cyclopentadiene, involving the heterocyclic ring. A 1,1′-diarsaferrocene was obtained by Ashe et al. [210].

A striking difference to pyridine is the lack of basicity and nucleophilicity for phosphabenzene and arsabenzene, which are protonated at the α- and γ-carbon atoms (this reaction is responsible for deuteration). Neither alkyl halides nor trialkyloxonium salts can alkylate phosphabenzene, therefore there will be no discussion of quaternary salts for these pnictogena-hetarenes. Whereas pyridine can be oxidized to the zwitterionic N-oxide, phosphabenzene affords non-aromatic λ^5-oxidation products **35** and **36** with tetracoordinated $P^{(V)}$ phosphorus atoms, similar to phosphinoxides and phosphonic acids, respectively.

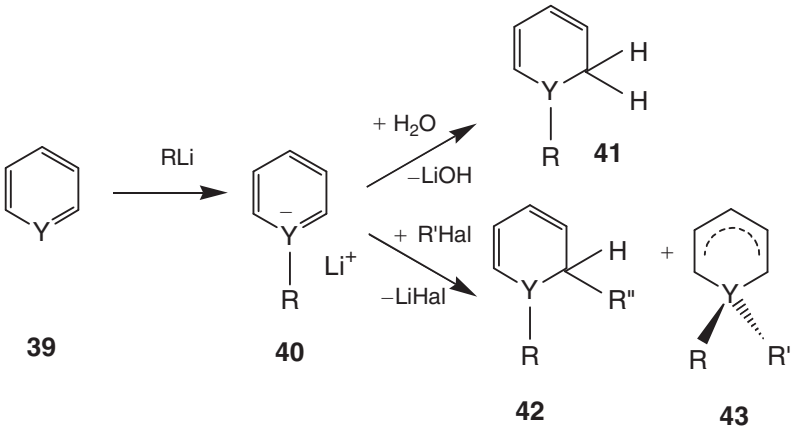


35 **36**

All pnictohetarenes with Y = P, As, Sb, and Bi react with dienophiles such as hexafluoro-2-butyne affording hetero-barrelene derivatives (P- at 100 °C, As- at 25 °C, Sb- and Bi-pnictohetarenes at even lower temperatures). The equilibrium low-temperature dimerizations of bismabenzene and stibabenzene (**37**–**38**) also involve such cycloadditions.

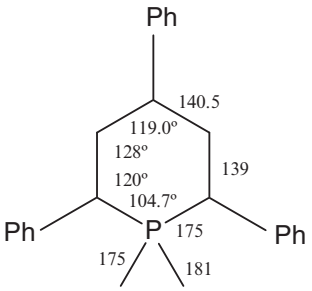
37 **38**

Strong nucleophiles such as organolithium or organomagnesium derivatives do not react with substituted or unsubstituted phosphabenzene or arsabenzene (**39**, Y = P or As) by nucleophilic substitution as in the case of pyridines, but by addition to the heteroatom forming intermediate anions **40**. These can then be converted into non-aromatic compounds by reaction with water to yield 1-alkyl-1,2-dihydro-derivatives **41**, or they can be alkylated by an alkyl halide with the same or a different alkyl group, when two products may result: a 1,2-dialkyl-1,2-dihydro 40-derivative **42**, or a λ^5-derivative **43**. The former products are kinetically controlled, whereas the latter compounds are thermodynamically controlled, so that one may favor the desired product by choosing the appropriate reaction conditions.



39 **40** **41** **42** **43**

Interestingly, the bond distances and angles of 1,1-dimethyl-2,4,6-triphenyl-λ^5-phosphorin (**44**) determined by X-ray diffraction are similar to those of λ^3-derivatives, yet the physical and chemical properties show that the λ^5-phosphorins are not aromatic, and that the tetra-coordinated phosphorus atom interrupts the ring current. However, Wong and Schleyer argued, from NICS values [215], that λ^5-phosphorins with highly electronegative P-bonded substituents (and thiabenzene with electronegative S-bonded substituents) may have residual aromaticity via hyperconjugative through-heteroatom conjugation.



44

The electronic structure of λ^5-phosphorins has an electron-rich conjugated five-carbon chain and a positively charged phosphorus atom, as attested by the ^{1}H-NMR and ^{13}C-NMR data, the 2,6-dideuteration that occurs easily, and the coupling with diazonium salts that leads to deep blue 2,6-bis-azo-dyestuffs. When the two phosphorus-bonded groups have structures that allow them to function as free-radical leaving groups (halogen, *tert*-butyl, benzyl), thermolysis of λ^5-phosphorins leads to aromatization, affording λ^3-phosphorins. Such aromatizations also take place on heating the 1,2- or 1,4-dihydro-derivatives at temperatures around 300 °C [216, 217].

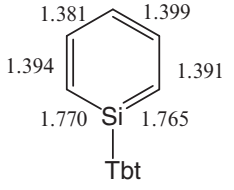
9 Group 14 Heterobenzenes (Silabenzene and Germabenzene)

This section will be fairly brief because silabenzene and its congeners are unstable under normal conditions, and can be studied only at low temperatures or by trapping in solid matrices. Only when Tokitoh and coworkers introduced bulky and effective steric protecting groups such as tris[bis(trimethylsilyl)methyl]phenyl or Tbt groups was it possible to obtain kinetic stabilization and study silabenzene and germabenzene derivatives as stable crystalline compounds under normal conditions [218–221].

T. J. Barton had succeeded earlier (in 1977) in isolating the first representative of this class, 1-methyl-silabenzene (silatoluene), and one year later the unsubstituted silbenzene [222–226]. Both compounds could only be studied in solid argon matrices at 10–23 K. Maier and coworkers using a different synthetic approach also studied the very unstable unsubstituted silabenzene, which was shown to react photochemically in the argon matrix [227–235].

Previous attempts by Märkl for kinetic stabilization had led to the synthesis of (i) 1,4-di-*tert*-butyl-1-silabenzene, which dimerized at 0 °C by a [2 + 2]-cycloaddition; (ii) 1,4-di-*tert*-butyl-2,6-bis(trimethylsilyl)-1-silabenzene, which was studied by NMR at low temperatures in special solvents; and (iii) 1-*tert*-butyl-2,6-bis-(di-methylisopropylsilyl)-4-trimethylsilyl-1-silabenzene, which was stable also only at very low temperatures [236–239]. Similar germabenzene derivatives were also obtained, and they were also unstable under normal conditions [240].

The kinetically stabilized Tbt-substituted silabenzene and germabenzene have planar rings, and bond lengths that attest their aromaticity. The geometry around the Si or Ge atom is completely trigonal [218–221]. Because the Tbt group is almost orthogonal to the heteroatomatic ring, the small differences between the lengths of the two sides of these rings are easy to account for.



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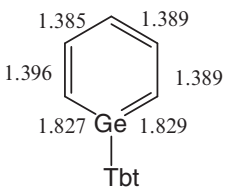

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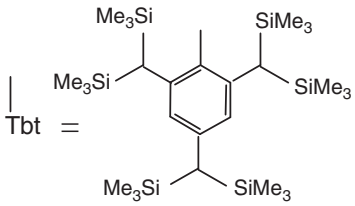
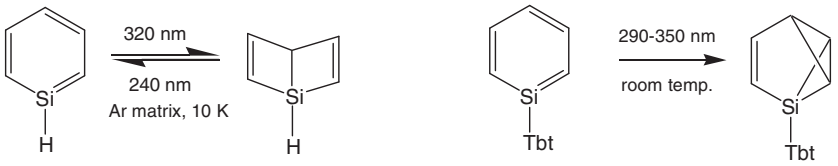


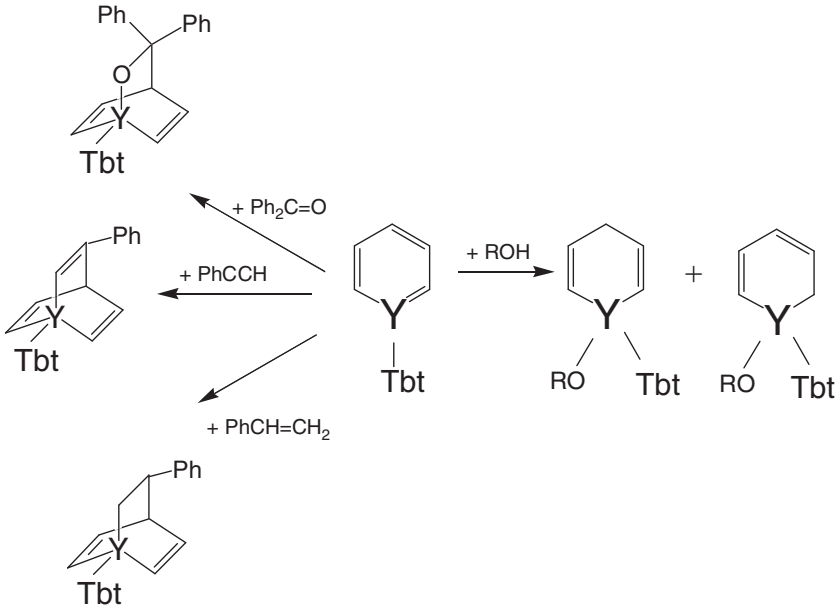
The NMR spectra involving the hetero-nucleus show low-field signals (93.6 ppm for the ^{29}Si atom of 1-Tbt-silabenzene, and 91.7 ppm for 1-Tbt-germabenzene) indicating the sp^2 character of the heteroatom. The ^{1}H-NMR and ^{13}C-NMR data also indicate aromaticity.

The stability of 1-Tbt-silabenzene (**49**) is confirmed by the fact that no dimerization was observed in hexane at 100 °C; however, on standing for 4 months in hexane solution, about half of the compound produced a [4 + 2] dimer, but on heating at 80 °C a retrocycloaddition took place. On irradiating with UV light (290–350 nm) in C_6D_6 at room temperature a benzvalenic valence isomer resulted, having the silicon atom with sp^3-hybridization (**50**). By contrast, the unsubstituted C_6H_6Si (**47**) afforded, at 10 K in argon matrix under the same photochemical excitation, a Dewar valence isomer (**48**), again having the silicon atom with sp^3-hybridization.



47 **48** **49** **50**

Despite the Tbt stabilization, the silabenzene and germabenzene are highly reactive towards water or alcohols (the RO residue adds to the heteroatom, and a hydrogen adds to a 2- or 4-carbon atom, destroying the aromaticity); benzophenone, styrene, and phenylacetylene afford bicyclo[2.2.2]octane-derivatives. In all these products, the heteroatom (Y = Si or Ge) has sp^3-hybridization.



1-Tbt-silabenzene and 1-Tbt-germabenzene react with metal carbonyl complexes $M(MeCN)_3(CO)_3$ (having M = Cr, Mo, or W) affording stable crystalline π-complexes that are stable under argon or in solid state. The calculated NICS(1) values are −9.1 ppm for the unsubstituted silabenzene and −9.1 ppm for the corresponding germabenzene, slightly lower than for benzene (−11.1 ppm).

Several reports on theoretical calculations have appeared for six-membered aromatic heterocycles involving one group 14 heteroatom [41, 42, 241–246]. Ottoson and coworkers calculated that π-electron-donor substituents in 2,4,6-positions could enhance the stability of these heterobenzenes [247], in addition to the steric bulk of the substituents, and inductive stabilization via *ipso*-silyl substitution by groups such as Tbt.

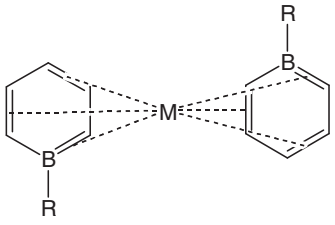
No stannabenzene or plumbabenzene could as yet be prepared.

10 Boratabenzene Anions and Related Compounds with Group 13 Elements

The first six-membered aromatic heterocycles containing one boron atom together with a second heteroatom (oxygen or nitrogen, namely boroxaro- and borazaro-derivatives, respectively) were prepared by Dewar and Pettit in 1955–1956 [248–250], and later it was proved that the seven-membered borepin has aromatic character. Borabenzene C_5H_5B, with six electrons in the valence shell of boron is too reactive to exist in condensed phase because it has a carbenic character. However, if it is connected to a neutral Lewis base derived from a tertiary amine, phosphine, or pyridine that becomes a positively charged group, then a stable zwitterionic (betainic) product results where the boron has a formal negative charge [234, 251]. Thus, tradition conserves the name borabenzene, which applies to a non-existent neutral molecule. However, boratabenzene C_5H_6B (or B-substituted derivatives thereof) as an independent ring is a stable aromatic molecule as an anion, in agreement with Table 2.

There is a certain analogy between the aromatic anions of cyclopentadienide ($C_5H_5^-$) and boratabenzene ($C_5H_6B^-$). 1-Methylbora-2,5-cyclohexadiene has a more acidic proton connected to the sp^3-hybridized ring carbon atom than cyclopentadiene, due to the same tendency of aromatic anion formation [252, 253]. The related 1-phenyl-1,4-dihydroborabenzene affords the lithium salt of 1-phenylboratabenzene on treatment with *tert*-butyllithium. Like metallic complexes such as ferrocene formed by cyclopentadiene, boratabenzene also forms such sandwich π-complexes with iron and cobalt. The iron complex can be acetylated under Friedel–Crafts conditions.

In 1970, Herberich first obtained cobalt metallic complexes of 1-phenyl- and 1-methyl-boratabenzene from $Co(C_5H_5)_2$ and $R–BHal_2$ [254–258]. Neutral complexes $Co(C_5H_5)(C_5H_5B–R)$ and $Co(C_5H_5B–R)_2$ are paramagnetic, and the corresponding cations are diamagnetic. Similar iron complexes were also obtained. Later, on treating such complexes with cyanide, Herberich prepared the first boratabenzene sodium and potassium salts. Complexes with Ru, Os, Rh, and Pt have also been obtained. The sandwich complex can have two boratabenzene rings (**51**), or one boratabenzene ring and one cyclopentadienide ring (**52**). Till now Herberich has published about 40 papers in the series entitled "Borabenzene derivatives." Only a few of them are cited here.



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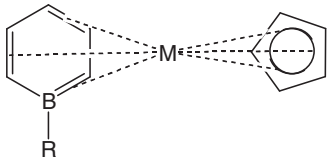
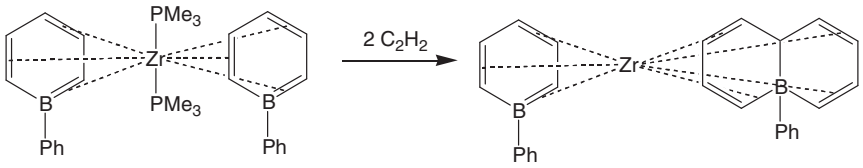


52

The molecular structures obtained by X-ray crystallography for the **51** sandwich complex with M = Co and R = Me and OMe show that both molecules have planar and parallel rings arranged centro-symmetrically, with interatomic bond distances C(α)–C(β) = 139 pm, C(β)–C(γ) = 141 pm, and C(α)–B = 152 pm [259]. Similar structures were found for metallic complexes with M = Fe or Mn, and R = Me or Ph [260].

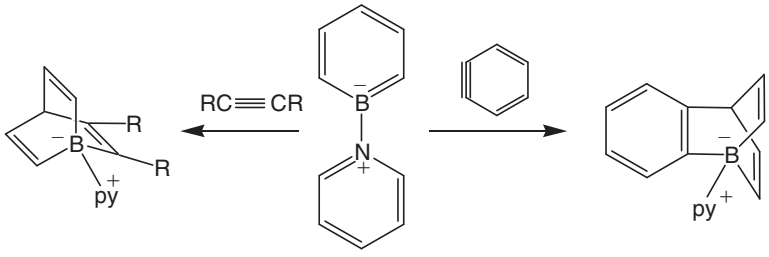
The molecular structure of the lithium 1-*H*-boratabenzene obtained by treating borabenzene-PMe_3 with $LiAlH_4$ indicates that the ring is planar, with the four C–C bond distances within the range 138–141 pm, but with slightly longer B–C bond distances (141–148 pm) [261]. On treating borabenzene-PMe_3 with a variety of nucleophiles such as lithium trimethylsilylacetylide, lithium dimethylamide, sodium ethoxide, and potassium diphenylphosphide, an associative mechanism via attack at the boron atom results in a nucleophilic substitution of the hydrogen attached to boron [262].

Starting from stannacyclohexadienes and $BHal_3$, Ashe and coworkers reported in 1971 a general synthesis of lithium boratabenzenes, which can easily be converted into other metal complexes [263–266]. The zirconium(IV) complexes with two boratabenzene rings and two halogen atoms have an electrophilic zirconium that is a good catalyst for alkene polymerization. The zirconium(II) complexes that have phosphine ligands instead of halogens (**53**) catalyze the incorporation of alkynes, leading to the formation of boratanaphthalene systems (**54**) [267].



53 **54**

Pyridine-stabilized borabenzenes **55** react with strong dienophiles such as benzyne or dimethyl acetylenedicarboxylate (R = COOMe) and afford 1-borabarrelenes **56** or **57**, respectively [268]. When the dienophile is fumaronitrile (*trans*-1,2-dicyanoethylene), this cycloaddition reaction is stereospecific, reversibly yielding a single diastereomer whose X-ray crystallographic analysis reveals the *trans*-configuration of the molecule.



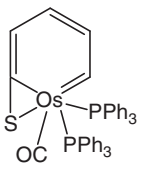
57 **55** **56**

Several quantum-chemical calculations have been published for borabenzene, its compounds with Lewis bases, and boratabenzene anions [269, and references cited therein].

Ashe et al. have obtained even a 1-arylgallatabenzene, a gallium congener, with the aryl group being 2,4,6-tri-*tert*-butylphenyl. ^{1}H-NMR and ^{13}C-NMR spectra confirm the aromatic delocalization. The acidity of the gallata-cyclohexadiene precursor is lower than that of the boron analog or cyclopentadiene, but higher than that of indene [271].

11 Metallabenzenes

Roald Hoffmann's 1982 Nobel Prize lecture was centered on the idea that transition metals are able to give rise to groups that are isolobal to common organic groups [272]. The term "isolobal" had been introduced in a paper by Elian, Chen, Mingos and Hoffmann in 1976 [273]. Groups with a metal M coordinated to halides (Hal) or to two-electron neutral ligands (such as CO or PR_3), for instance ML_3 or ML_2Hal_2 groups with M = Co, Rh, Ir, or also ML_4 groups with M = Mn, Re (which are isolobal to sp^2-hybridized CH groups), were predicted in 1979 to be able to become part of six-membered aromatic rings [274]. Indeed, 3 years later Roper and coworkers (all his papers have alphabetically ordered authors) obtained the first metallabenzene **58** having an octahedrally coordinated osmium atom [275, 276]. The synthesis involved the pentacoordinated complex $Os(CO)(CS)(PPh_3)_3$ and two acetylene molecules, via the loss of one triphenylphosphine molecule and incorporation of the CS ligand. An iodo-derivative **59** with a true osmabenzene ring was also obtained. Methylation of **58** with methyl iodide afforded a thioether **60** which, on treatment with electrophiles E, underwent typical electrophilic substitutions in *para* position relative to the SCH_3 substituent, affording substituted compounds **61**: E = NO_2 (via cupric nitrate and acetic anhydride), Cl (via $PhICl_2$), or Br (via Br_2 and iron powder). The X-ray crystallographic data show that the rings are planar, and the two phosphine ligands are on a line that is perpendicular to this plane. Bond lengths to the metal are about 200 pm, and all C–C bond lengths are within the range 136–140 pm, denoting aromatic electronic delocalization.



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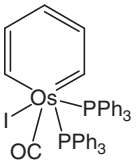

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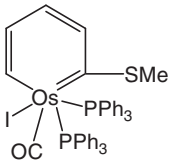

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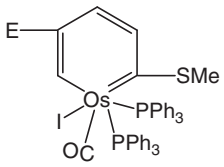


61

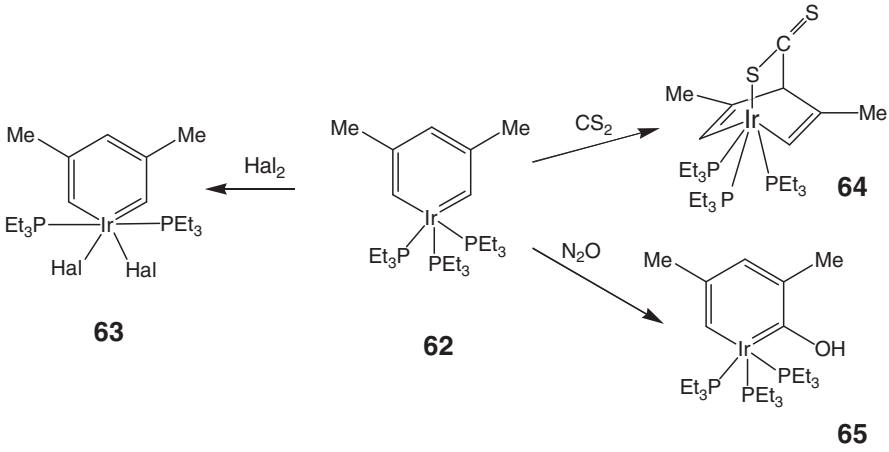
Subsequent experimental work benefited from new synthetic approaches: for the C_5-chain, Hughes and coworkers used vinylcyclopropenes [277, 278]; Bleeke et al. used potassium 2,4-dimethylpentadienides [279–281]; and Jia with coworkers used

3-hydroxy-1,4-pentadiyne [281–284]. Alternatively, a C_4-fragment can be combined with one carbon from a ligand, which may be CO [285, 286]. Roper's synthesis involved two acetylene molecules and the mechanism probably involved the association of one of them with the M-CS fragment to form a metallacyclobutene intermediate that reacted further with the second acetylene molecule. Finally, three alkyne molecules may react with the metal center followed by oxidation and ring contraction [287].

So far, the metals that have successfully been incorporated into metallabenzenes are Os, Ir, and Pt, with Ru as the only lighter metal. Comprehensive reviews have been published recently by Landorf and Haley [288], by Bleeke [289, 290], by Wright [291], and by Fernandez and Frenking [292].

All NMR data support the idea that the platinum family metals give rise to authentically aromatic systems. The large downfield chemical shifts of protons connected to α-carbon atoms (in the range 10–14 ppm) are due both to ring currents and to the magnetic anisotropy of the metal according to the McConnell equation. Proton chemical shifts for β- and γ-CH groups appear in the usual range, at around 7 ppm. Similar effects are observed in the ^{13}C-NMR spectra.

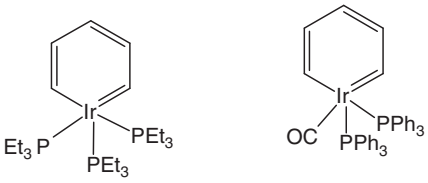
With cyclopentadiene, metallabenzenes form η^6-complexes, which stabilize the structures. Iridabenzene **62** (a red crystalline solid, stable indefinitely at room temperature under nitrogen) undergoes reactions that are uncharacteristic for aromaticity: rearrangements of the metallabenzenic six-membered ring to an aromatic cyclopentadienide ring, which forms a semisandwich π-complex with the metal; cycloaddition with carbon disulfide to a bicyclo[2.2.2]octadienic structure **64**; ligand exchange halogenation with Cl_2 or Br_2 (**63**); and oxidation with nitrous oxide (via an irida-benzoepoxide) to an iridaphenol **65** that does not tautomerize to a carbonylic form [285].



The X-ray crystal structure of **62** presents a square pyramidal coordination geometry, with a planar C_5-chain and the iridium atom slightly displaced (by 24 pm) out of this plane [279, 293].

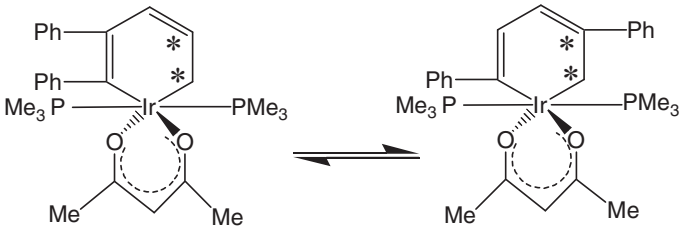
Iridabenzene derivatives **66** with pentacoordinated iridium have NMR spectra that prove rapid equilibration of the trigonal-bipyramidal ligands, probably by the

Berry turnstile pseudorotation mechanism. Interestingly, with an excess of less sterically demanding nucleophiles such as PMe_3, PPh_3, or $P(OMe)_3$, only one of the phosphine ligands is substituted, yielding **67** when the nucleophile is carbon monoxide, probably by a dissociative mechanism [293].



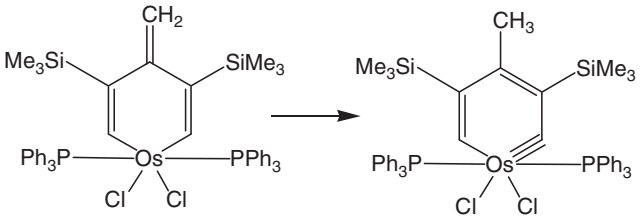
66 **67**

For an octacoordinated iridium acetylacetonato derivative that is no longer aromatic, an interesting rearrangement of the diphenylpentadienic moiety was observed by means of isotopic labeling with ^{13}C (asterisks) [294, 295].



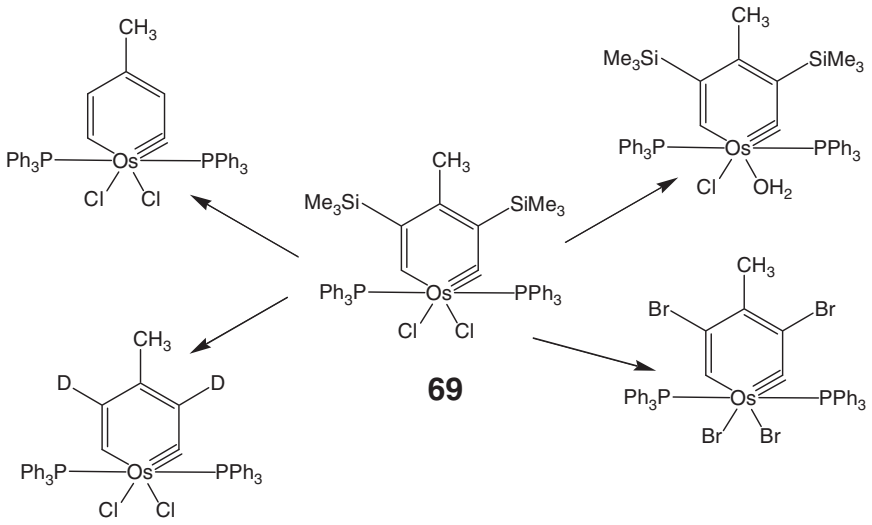
For various metallabenzenes with Fe, Re, Ru, Rh, Pd, Os, Ir, and Pt, free energies for the conversion into energetically favored cyclopentadienyl semisandwich systems as well as the fairly high activation barriers have been calculated by DFT methods [296]. Also, DFT calculations involving the four occupied π molecular orbitals (benzene has only three such occupied orbitals) provide an understanding of the slight deviation of the metal from the plane of the aromatic ring [284].

By treating a silylated methylene-osmacyclohexadiene **68** with acids, Jia and coworkers obtained the first stable osmabenzyne **69** with a planar ring having the triple Os–C(*sp*) bond distance of 181.5 pm and the Os–C(sp^2) bond of 193.9 pm [282, 297].



68 **69**

This osmabenzyne **69** could be converted into other osmabenzynes: with HBF_4 it is desilylated, with deutero-triflic acid it affords a dideutero-derivative, with excess bromine it produces a tetrabromo-derivative, and on longer treatment with HBF_4 an aquo-complex was formed.



An intriguing iso-osmabenzene with an allenic (1,2,4-cyclohexatrienic) structure was reported; its X-ray crystallographic determination confirmed the presence of an *sp*-hybridized carbon atom in the ring [298]. Martin and coworkers surveyed the criteria for judging the aromaticity of various metallabenzenes (resonance energy, molecular structure, electronic structure, magnetic resonance, chemical reactivity), concluding that whereas aromaticity is undoubtedly present, metallabenzenes show specific reactions such as the formation of a cyclopentadienyl semi-sandwich metal complex [299].

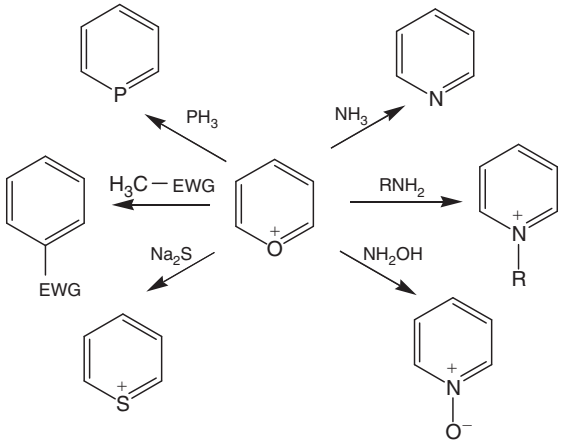
The field of metallabenzenes is under active investigation, with numerous reports being published each year. A brief listing of references that have not been cited above is given according to the metal: ruthenabenzenes [300–302], platinabenzenes [303, 304], iridabenzenes [305], osmabenzenes [306]. Haley and coworkers observed that in some instances the formation of metallabenzenes from vinylcyclopropenes competes with valence-isomeric benzvalenic structures [307, 308] (for a systematic survey of valence isomers of annulenes an earlier three-volume book may be consulted [309]).

12 Conclusions

The bottom line on monocyclic six-membered aromatic compounds is that, so far, only benzene, the azines with one through four nitrogen atoms, phosphabenzene and arsabenzene, pyrylium, azapyrylium and chalcogenopyrylium cations (with or

without exocyclic groups such as hydroxy, amino and corresponding tautomeric or prototropic forms), and the metallabenzenes with platinum family metals have been proved to afford stable molecules under normal conditions. Other heteroatoms give rise to marginally aromatic and much less stable compounds. Stabilizing metallic complexes or substituents with significant electronic or steric effects are likely to enlarge this list.

In the following chart of converting pyrylium salts (usually with substituted α-positions) into other six-membered ring systems, there results an increase in aromaticity. For any conversion associated with decreasing aromaticity one must employ "energy-rich reagents" (such as in the conversion of pyridine into pyrylium, which requires treatment of pyridine with sulfur trioxide or chlorosulfonic acid to afford the zwitterionic compound **22** with EWG = SO_3^-; this is followed by treatment with sodium methoxide affording the sodium salt of glutacondialdehyde **23**; the final product is obtained by treatment with anhydrous strong acids such as a solution of perchloric acid in dichloromethane – caution is necessary because of the danger of explosion associated with such solutions and with the unsubstituted pyrylium perchlorate).



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Chemistry of Hetero Analogs of Pentalene Dianion

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Abstract This chapter is devoted to recent progress in the chemistry of the 5:5 fused heterocyclic systems. There are four possible modes of 5:5 fusions of the simple five-membered heterocycles leading to four structures containing one heteroatom in each ring. The heteroatoms may be the same or different and may be O, NH, S, Se, Te, P, As, or Sb. The fully conjugated hetero analogs of pentalene dianion have a central C–C bond and are isoelectronic with the 10-π-electron pentalene dianion. The scope of the chapter is outlined with a survey of various structural types and nomenclature of the parent compounds and their derivatives. New synthetic procedures and synthetic applications of title compounds are presented. This review has concentrated on the new developments achieved from 1997 to September 2007.

Keywords Diheteropentalene systems, 5, 5-Fused heterocycles aromaticity, 5, 5-Fused heterocycles reactivity, Ring syntheses

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Contents

Abbreviations and Symbols

Ac	Acetyl
AIBN	Azobis(isobutyronitrile)
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPE	1,2-Bis(diphenylphosphino)ethane
EWG	Electron withdrawing group
LDA	Lithium diisopropylamide
MCPBA	*m*-Chloroperbenzoic acid
MW	Microwave
NBS	*N*-Bromosuccinimide
NPMI	*N*-Phenylmaleimide
PPA	Polyphosphoric acid
Ph	Phenyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tol	Tolyl
Ts	Tosyl

1 Introduction

This chapter covers bicyclic ring systems containing two five-membered rings where each ring contains one heteroatom and neither heteroatom is situated at the position of the ring junction. These 5:5 fused heterocyclic systems are represented by the general structures **l–4**, wherein X and Y may be the same or different heteroatoms and represent O, NH, S, Se, and Te. The fully conjugated title compounds have a central C–C bond and are isoelectronic with the 10-π-electron pentalene dianion **5** (Fig. 1).

The chemistry of hetero analogs of dipentalene dianion has been reviewed in *Comprehensive Heterocyclic Chemistry* I–III [1–3]. The interest in these systems continues. Both aromatic and nonaromatic systems are considered. The number of compounds is potentially huge, yet it will become obvious that the most work has been carried out on systems with N, S, Se, and O as the heteroatoms. A smaller number of compounds exist where Te is incorporated into ring systems. These four general classes of heterocycle **l–4** are referred to as 1,4-diheteropentalenes **1**, 1,5-diheteropentalenes **2**, 1,6-diheteropentalenes **3**, and 2,5-diheteropentalenes **4**, or generally as A,B-diheteropentalenes.

The parent hetero analogs of dipentalene dianion **5** possess a different degree of aromaticity depending upon chemical properties such as their ability to give electrophilic substitution reactions. Generally one can state that they belong to the electron-rich heterocycles, and efforts to compare of their relative aromaticity have been published [4–7]. Substituents attached to, or benzene ring fusion to, the title structures influences the aromaticity. Most of the available criteria point to an order of decreasing aromaticity of 1,4 >1,6 >1,5 >2,5 ring system, which is influenced by the heteroatom in the order S >Se ≥ N >O [2].

The progress in the chemistry of such compounds is based on their utilization in tuning properties of organic polymers at the molecular level [8]. Tuning is typically accomplished through synthetic modifications, which permits the incorporation of side-chain functionalities. The use of some title fused-ring precursors has been found to be a powerful approach to the preparation of new low band gap, conjugated polymers. In particular, various thieno[3,4-*c*]thiophenes **6**, thieno[3,2-*b*]thiophenes **7**, thieno[3,2-*b*]pyrroles **8**, pyrrolo[3,2-*b*]pyrroles **9**, dithieno[3,2-*b*:2′,3′-*d*]thiophenes **10**, dithieno[3,2-*b*:2′,3′-*d*]pyrroles **11**, and dipyrrolo[3,2-*b*:2′,3′-*d*]thiophenes **12** have been investigated (Fig. 2).

Thieno[3,4-*c*]thiophenes **6** have attracted much attention from both theoretical and spectroscopic viewpoints as 10-π-electron heterocycles with nonclassical structures [1–3]. However, the synthesis of thieno[3,4-*c*]thiophenes is not easy. This chapter surveys known compounds of this type and their methods of synthesis.

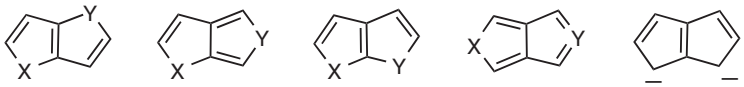


Fig. 1 General structures of A,B-heteropentalene systems

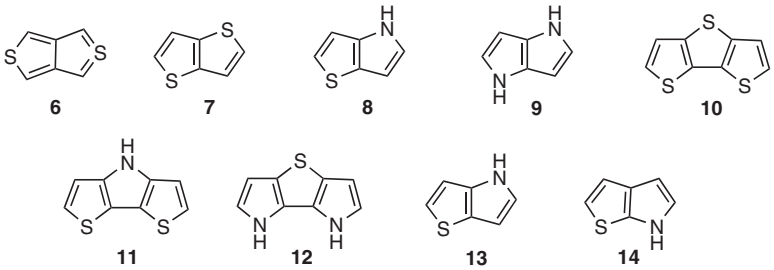
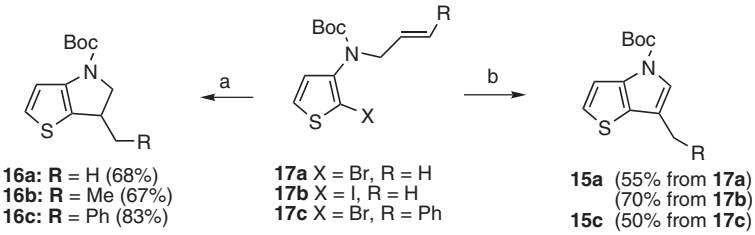


Fig. 2 The 5:5 fused heterocyclic systems



Scheme 1 **a** Bu_3SnH, AIBN, toluene, reflux; **b** $Pd(PPh_3)_4$, K_2CO_3, DMF, 60 °C [9]

2 1,4-Diheteropentalene Systems

2.1 Synthesis of 1,4-Diheteropentalene Systems

The syntheses of this type of compound are almost always based on construction of the second heterocyclic ring onto an existing heterocycle.

Thieno[3,2-*b*]pyrroles **15** and 5,6-dihydrothieno[3,2-*b*]pyrroles **16** were prepared by cyclization of *tert*-butyl-2-allyl- and *N*-allyl-3-thienylcarbamates **17** (Scheme 1). Pd-catalyzed cyclization of **17a–c** has allowed access to thieno[3,2-*b*]pyrroles **15**. The radical route has led to the formation of 5,6-dihydrothieno[3,2-*b*]pyrroles **16** [9]. The iodothiophene derivative **17a** was a better substrate than the bromo analog **17a** for access to **15a**.

Flash vacuum pyrolysis at 650 °C of thiophene acrylate **18** and malonate **19** afforded annelation of a furan ring onto a thiophene giving 2-(methylsulfanyl)thien o[3,2-*b*]furan **20** and methyl 5-(methylsulfanyl)thieno[3,2-*b*]furan-2-carboxylate **21**, respectively, in yields of 21% and 22% (Fig. 3) [10].

Methyl 2-[3-(trifluoromethyl)phenyl]-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate **22** was obtained by thermolysis of the corresponding methyl 2-azido-3-{5-[3-(trifluoromethyl)phenyl]-2-furyl}propenoate **23**, which was formed by condensation of 5-[3-(trifluoromethyl)phenyl]furan-2-carbaldehyde **24** with methyl azidoacetate under sodium methoxide catalysis (Scheme 2) [11].

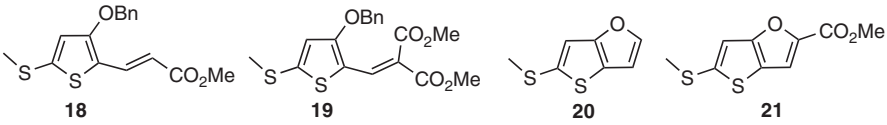
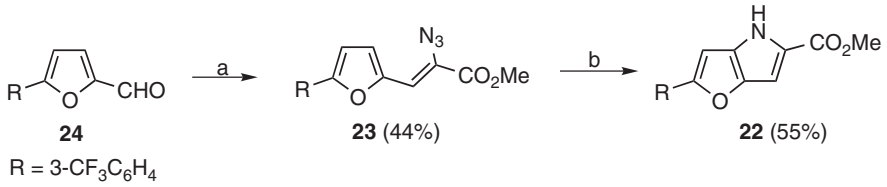
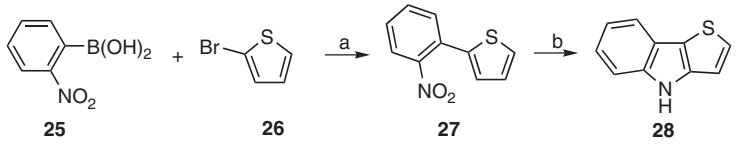


Fig. 3 Ethyl 3-[3-(benzyloxy)-5-(methylsulfanyl-2-thienyl]acrylate **18**, dimethyl{[3-(benzyloxy)-5-(methylsulfanyl-2,thienyl]methylene}malonate **19**, 5-(methylsulfanyl)thieno[3,2-*b*]furan **20** and methyl 5-(methylsulfanyl)thieno[3,2-*b*]furan-2-carboxylate **21**



Scheme 2 **a** $N_3CH_2CO_2Me$, MeONa; **b** reflux, toluene [11]

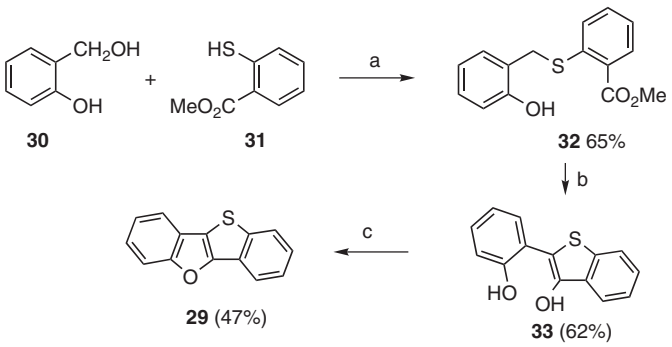


Scheme 3 **a** $Pd(Ph_3P)_4$, $NaHCO_3$, DMF–H_2O (1:1), MW, 15 min; **b** $(EtO)_3P$, MW, 15 min [13]

An easy access to thieno[2,3-*b*]indole was found by Miyaura and coworkers [12] using a microwave-enhanced cross-coupling reaction in combination with a microwave-assisted Cadogan reductive cyclization. The authors [13] stated that their method is very useful in minimizing the proto-deboronation in the cross-coupling reaction, and enhances the rate of reductive cyclization in a dramatic manner.

2-Nitrophenylboronic acid **25** and 2-bromothiophene **26** were successfully cross-coupled in 15 min under microwave irradiation in a good yield into 2-(2-nitrophenyl)thiophene **27**, which by reductive cyclization gave, in good yield, 4*H*- thieno[3,2-*b*]indole **28** (Scheme 3).

A synthesis of the [l]benzothieno[3,2-*b*][l]benzofuran **29** based on the formation of the furan ring in the key step was elaborated. Alkylation of methyl 2-sulfanybenzoate **30** with 2-hydroxybenzyl alcohol **31** was effected using freshly prepared ZnI_2 in DCM; an intermediate **32** was obtained. Cyclization with LDA in THF afforded **33**, which by subsequent cyclodehydratation with PPA gave **29** in moderate yield (Scheme 4) [14].



Scheme 4 **a** ZnI_2, DCM; **b** LDA, THF, **c** PPA [14]

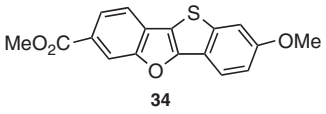
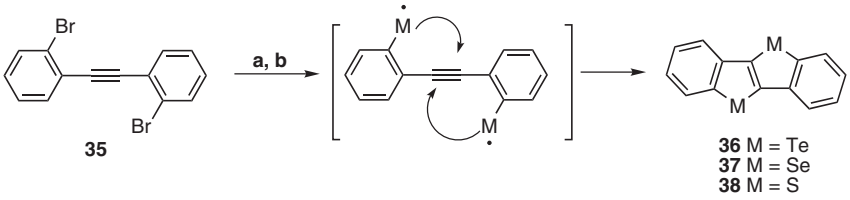


Fig. 4 Methyl 8-methoxy[l]benzothieno[3,2-*b*][l]benzofuran-3-carboxylate **34** [14]

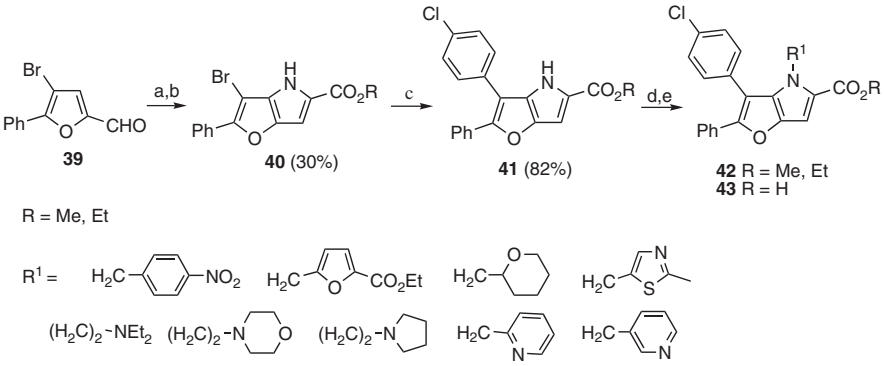


Scheme 5 **a** Bu^{t}Li; **b** M [l5]

According to the above procedure, the compound **34** was made as a new type of core for ferroelectric crystals (Fig. 4) [14].

A double heterocyclic ring formation was also described. Treatment of 2,2′-dibromodiphenylacetylene **35** with *tert*-butyllithium followed by tellurium insertion resulted in intramolecular ring closure to afford [l]benzotelluro[3,2-*b*][l]benzotellurophene **36** (Scheme 5). Similarly, [l]benzoseleno[3,2-*b*][l]benzoselenophene **37** and [l]benzothieno [3,2-*b*][l]benzothiophene **38** were also obtained [15].

Milkiewicz and coworkers [16] prepared a series of novel tetra-substituted furo[3,2-*b*]pyrroles from the methyl or ethyl 3-bromo-2-phenylfuro[3,2-*b*]pyrrole-5-carboxylate **40**, which was prepared from 3-bromo-2-phenylfuran-2-carbaldehyde **39**. The compounds **40** were subjected to a Suzuki coupling with 4-chlorophenyl boronic acid to form **41**, which was treated with a variety of alkylating agents to afford the corresponding esters **42**. The esters were then saponified to acids **43** (Scheme 6).



Scheme 6 **a** Ethyl or methyl azidoacetate, EtONa, or MeONa; **b** toluene, reflux, 30%; **c** 4-chlorophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH, 82%; **d** R^1-bromide or chloride, NaH, NaI, 60 °C, 16 h; **e** NaOH, EtOH, 50 °C, 4 h, 16–88% (**42**), quant (**43**) [16]

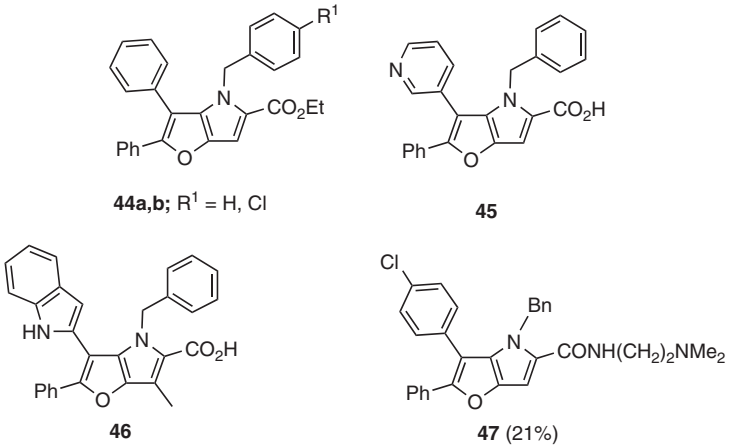


Fig. 5 Ethyl 4-benzyl-2,3-diphenylfuro[3,2-*b*]pyrrole-5-carboxylate **44a**, ethyl 4-(4-chlorobenzyl)-2,3-diphenylfuro[3,2-*b*]pyrrole-5-carboxylate **44b**, 4-benzyl-2-phenyl-3-(pyridin-3-yl)furo[3,2-*b*]pyrrole-5-carboxylic acid **45**, 4-benzyl-3-(indol-2-yl)-6-methyl-2-phenyl furo[3,2-*b*]pyrrole-5-carboxylic acid **46**, 4-benzyl-3-(4-chlorophenyl)-2-phenylfuro[3,2-*b*]pyrrole-5-[*N*-(2-*N*,*N*-dimethylethyl)]carboxamide **47** [16]

It was found that the order of reactions could be reversed, with the N-alkylation performed prior to the Suzuki reaction. In this way compounds **44a,b** were synthesized. The synthesis of compounds **45–47** is also described (Fig. 5) [16].

2.2 Reactions of 1,4-Diheteropentalene Systems

2.2.1 Electrophilic Attack at Carbon

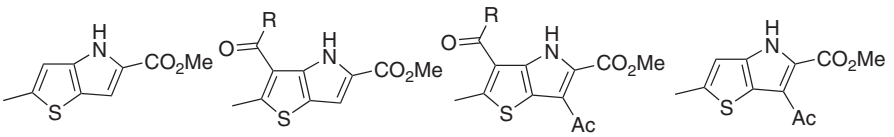
Electrophilic reactions at carbon have been described [1, 2]. They take place preferably at 2,5-positions, i.e., at α-position of the simple heterocycles. If these positions are occupied, reactions take place at positions C-3 and C-5.

The influence of catalysts ($AlCl_3$ and $SnCl_4$), acid chlorides, and solvents (dichloroethane, nitromethane) in the acylation of methyl 2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **48** was studied [17]. Conditions for the regioselective acylation processes were found and thus were obtained four types of compounds **49a–f**, **50a–e** and **51** (Fig. 6).

For the first time the thienopyrrole-based photochrome **53** was synthesized from **48c** via the intermediate **52** (Scheme 7) [17].

2.2.2 Electrophilic Attack at Nitrogen

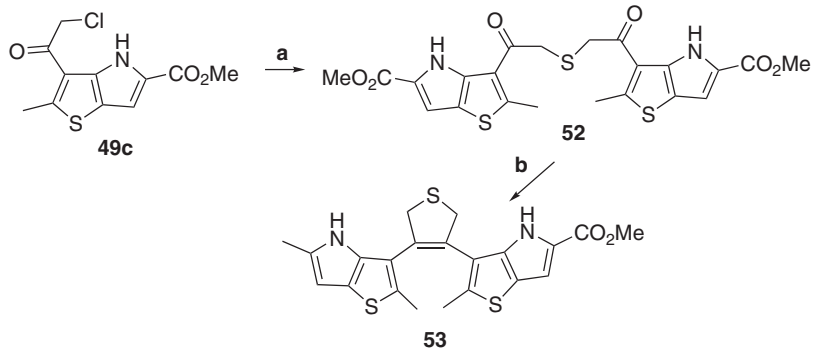
The possibility of acetylating the pyrrole nitrogen atom in **48** was investigated. The reaction was performed in the presence of different bases, and the highest yield of the corresponding compound **54** (Fig. 7) was achieved with potassium *tert*-butoxide



48 **49a-f** (63-77%) **50a-e** (62-78%) **51** (93%)

R		R		R		R	
49a	Me	**49d**	$CHCl_2$	**50a**	Me	**50d**	$CHCl_2$
49b	Et	**49e**	CCl_3	**50b**	Et	**50e**	CCl_3
49c	$ClCH_2$	**49f**	Pr^i	**50c**	$ClCH_2$		

Fig. 6 Methyl 2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **48**, methyl 3-acetyl-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **49a**, methyl 2-methyl-3-propanoyl-4*H*-thieno [3,2-*b*]pyrrole-5-carboxylate **49b**, methyl 3-chloroacetyl-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **49c**, methyl 3-dichloroacetyl-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **49d**, methyl 2-methyl-3-trichloroacetyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **49e**, methyl 2-methyl-3-(2-methylpropanoyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **49f**, methyl 3,6-diacetyl-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **50a**, methyl 6-acetyl-2-methyl-3-propanoyl-4*H*-thieno [3,2-*b*]pyrrole-5-carboxylate **50b**, methyl 6-acetyl-3-chloroacetyl-2-methyl-4*H*-thieno [3,2-*b*]pyrrole-5-carboxylate **50c**, methyl 6-acetyl-3-dichloroacetyl-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **50d**, methyl 6-acetyl-2-methyl-3-trichloroacetyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **50e**, methyl 6-acetyl-2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **51** [17]



Scheme 7 **a** Na_2S; **b** $TiCl_4$, Zn [17]

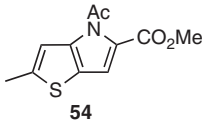
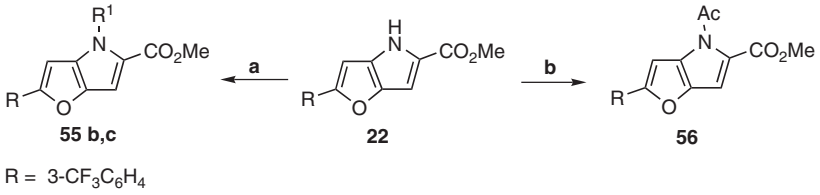


Fig. 7 Methyl 4-acetyl-2-methylthieno[3,2-*b*]pyrrole-5-carboxylate **54** [17]

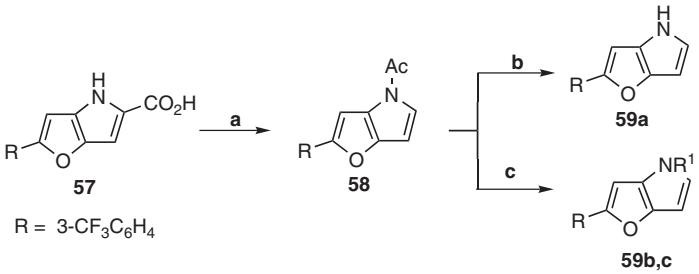


Scheme 8 **a** R^1–X, X = I, Cl; R^1 = Me, Bn, benzyltriethylammonium chloride, NaOH, toluene, 60 °C; **b** Ac_2O [18]

[17]. As expected, even trace amounts of this compound **54** are absent from the acylation products of thienopyrrole **48** under the Friedel–Crafts conditions [17].

Phase transfer catalysis was found [1, 2] to be successful for N-substitution of the furo[3,2-*b*]pyrrole system. The reaction of **22** with methyl iodide or benzyl chloride gave derivatives **55b,c**. Methyl 4-acetyl-2-[3-(trifluoromethyl)phenyl]furo [3,2-*b*]pyrrole-5-carboxylate **47** was obtained by refluxing of **22** in acetic anhydride (Scheme 8) [18].

4-Acetyl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*b*]pyrrole **58** was obtained by refluxing in acetic anhydride 2-[3-(trifluoromethyl)phenyl]-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid **57** and it was used for preparation of parent **59a** and of the N-substituted compounds **59b,c** (Scheme 9) [18].



Scheme 9 **a** Ac_2O; **b** NaOH, ethanol; **c** R^1–X, X = I, Cl; R^1 = Me, Bn, benzyltriethylammonium chloride, NaOH, toluene, 60 °C [18]

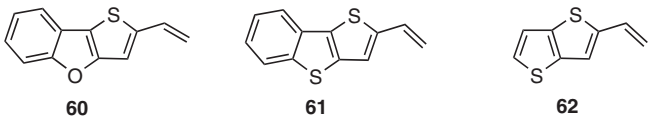


Fig. 8 2-Vinylthieno[3,2-*b*][1]benzofuran (**60**), 2-vinyl[1]thieno[3,2-*b*][1]benzothiophene (**61**), 2-vinylthieno[3,2-*b*]thiophene (**62**)

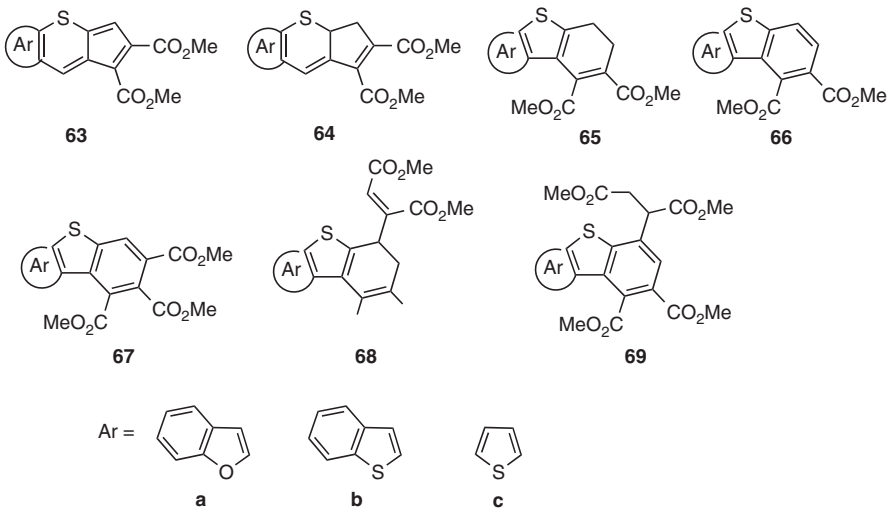


Fig. 9 Structures of the isolated products **63–69** [19]

2.2.3 Cycloaddition Reactions

A reactivity study of compounds **60–62** (Fig. 8) was performed by Svoboda and coworkers [19].

Cycloaddition reactions were performed by heating of **60–62** with dimethyl acetylene dicarboxylate (DMAD) in toluene to reflux under a nitrogen atmosphere. The structures of the isolated products **63–69** are depicted in Fig. 9. Their yields are summarized in Table 1.

Table 1 Products of the cycloaddition reactions and their yields (%) [19]

63a	19	**64a**	16	**65a**	20	66a	20	**67a**	17	**68a + 69a**	3
63b	10	**64b**	11	**65b**	25	**66b**	21	**67b**	23	**68b + 69b**	2
63c	10	**64c**	4	**65c**	9	**66c**	11	**67c**	9	**68c + 69c**	6

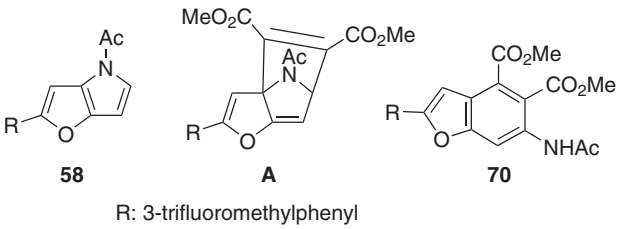


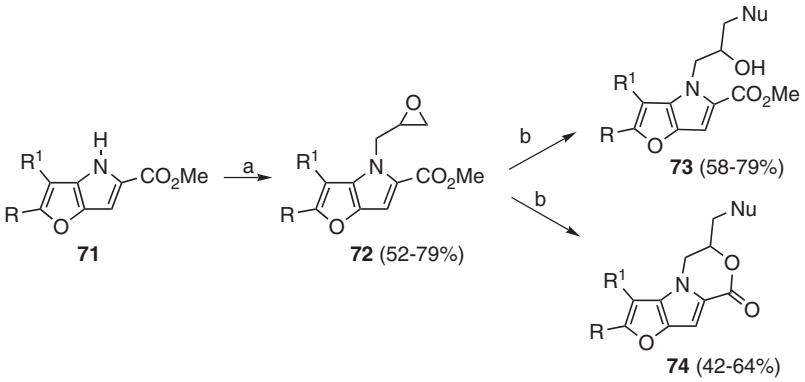
Fig. 10 4-Acetyl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*b*]pyrrole **58**, dimethyl 6-acetylamino-2-[3-(trifluoromethyl)phenyl]-1-benzofuran-3,4-dicarboxylate **70** [18]

The reactions of the furo[3,2-*b*]pyrroles and their benzo derivatives with DMAD were described earlier [2] and it was stated that the reaction course is influenced by the ring substituents. Recently, it was found that the 4-acetyl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*b*]pyrrole **58** reacts in acetonitrile with DMAD at the a and α′ -positions of the pyrrole ring, giving [4 + 2] cycloadduct, which by subsequent 1,5-sigmatropic rearrangement gives the substituted benzo[*b*]furan **70** (Fig. 10) [18]**.**

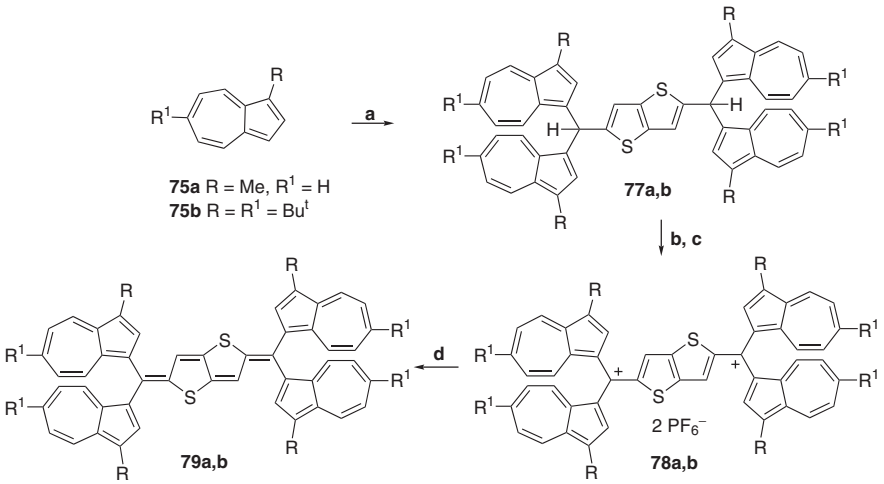
2.2.4 Reaction of Substituents Attached to 1,4-Diheteropentalene Systems

Methyl 4-oxiranylmethylfuro[3,2-*b*]pyrrole-5-carboxylates **72** were prepared by reaction of the appropriate starting derivatives of **71** with an excess of 2-chloromethyloxirane. The compounds **72**, on reaction with heterocyclic amines (morpholine, pyrrolidine, piperidine or 4-methylpiperazine), undergo oxirane ring opening giving *N*-2-hydroxy-3-heteroaminopropyl substituted compounds **73** or substituted 4,5-dihydrofuro[2′,3′:4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-ones **74** (Scheme 10). The formation of compounds **74** is a result of intramolecular reaction of the newly formed OH group with the CO_2Me group present at C-5 of the furo[3,2-*b*]pyrrole unit, with loss of MeOH [20].

The stable di(1-azulenyl)thieno[3,2-*b*]thiophene-2,5-diyl spacers **78a** and **78b** were prepared by hydride abstraction of the corresponding 2,5-bis[bis(methyl and 3,6-di-*tert*-butyl-1-azulenyl)methyl]thieno[3,2-*b*]thiophenes **77a** and **77b**, the synthesis of which was established by the reaction of 1-methyl- and 1,6-di-*t*-butylazulenes **75a** and **75b** with thieno[3,2-*b*]thiophene-2,5-dicarbaldehyde **76** (Scheme 11). The dications **76** showed high stability with large pK_R^+ values. The electrochemical behavior of **78** was examined by cyclic voltammetry (CV). Chemical reduction of **78** with Zn powder in acetonitrile afforded **79** as deep-colored crystals, which exhibited rather high



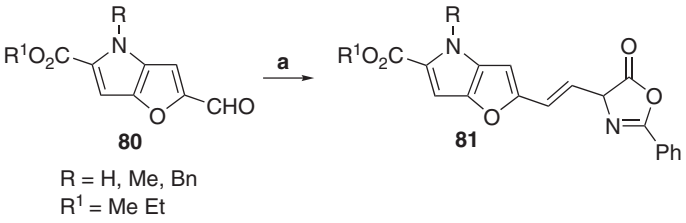
Scheme 10 **a** 2-Chloromethyloxirane; R = H, Me, Ph; R^1 = H, Me; **b** Nu: piperidin-1-yl, pyrrolidin-1-yl, morpholin-4-yl, 4-methylpiperazin-1-yl [20]



Scheme 11 **a** Thieno[3,2-*c*]thiophene-2,5-dicarbaldehyde **76**, AcOH; **b** DDQ; **c** HPF_6; **d** electrochemical reduction or Zn powder in MeCN [21]

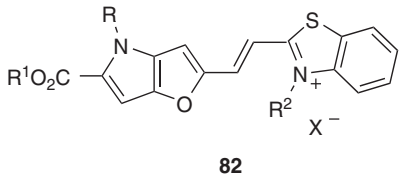
electron-donating ability [21]. Formation of the thienoquinoid products **79** from **78** was characterized by UV–vis spectroscopy under electrochemical reduction conditions.

The condensation products of furo[3,2-*b*]pyrrole type aldehydes **80a–d** with hippuric acid were obtained in dry acetic anhydride catalyzed by potassium acetate, as shown in Scheme 12. The products methyl-2-[(*E*)-(5-oxo-2-phenyl-1,3-oxazol-5(4*H*)-ylidene)methyl]furo[3,2-*b*]pyrrol-5-carboxylates **81a–d** were obtained in yields of 53–90%. The course of the reaction was compared with the reaction of



81	R	R1
a	H	Me
b	H	Et
c	Me	Et
d	Bn	Et

Scheme 12 **a** $PhCONHCH_2CO_2H$, Ac_2O, AcOK [22]



82	R	R1	R2	X
a	H	Me	Me	I
b	H	Me	Bn	Br
c	Me	Et	Bn	Br
d	Bn	Et	Bn	Br

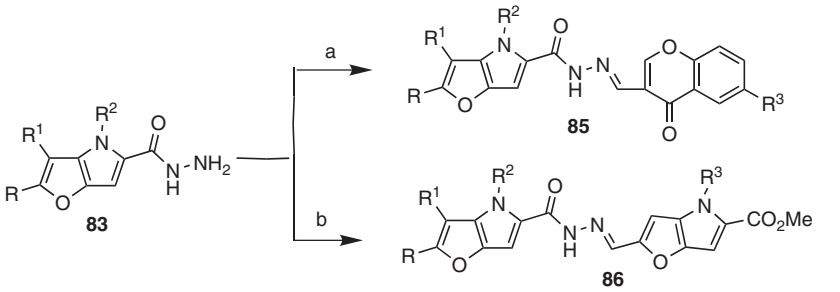
Fig. 11 2{(*E*)-2-[5-(Methoxycarbonyl)-4*H*-furo[3,2-*b*]pyrrol-2-yl]vinyl}-3-methyl-1,3-benzothiazolium iodide **82a**, 3-benzyl-2{(*E*)-2-[5-(methoxycarbonyl)-4*H*-furo[3,2-*b*]pyrrol-2-yl]vinyl}-1,3-benzothiazolium bromide **82b**, 3-benzyl-2{(*E*)-2-[5-(ethoxycarbonyl)-4-methylfuro[3,2-*b*]pyrrol-2-yl]vinyl}-1,3-benzothiazolium bromide **82c**, 3-benzyl-2{(*E*)-2-[5-(ethoxycarbonyl)-4-bezylfuro[3,2-*b*]pyrrol-2-yl]vinyl}-1,3-benzothiazolium bromide **82d** [23]

5-arylated furan-2-carbaldehydes with hippuric acid. It was found that the carbonyl group attached at C-2 of the fused system **80** is less reactive than the carbonyl group in 5-arylated furan-2-carbaldehydes in this reaction [22]. The configuration of the carbon–carbon double bond was determined using 2D NMR spectroscopic measurements and confirmed pure (*E*) isomers as products.

The condensation reaction of selected furo[3,2-*b*]pyrrole aldehydes **80** with benzothiazolium salts was carried out in refluxing methanol with pyridine as catalyst, giving **82a–d** (Fig. 11) [23].

Substituted hydrazones **85** and **86** were synthesized by the reaction of the corresponding furo[3,2-*b*]pyrrole-5-carbohydrazides **83** with 6-substituted-4-oxochromene-3-carbaldehydes **84** and methyl 2-formylfuro[3,2-*b*]pyrrole-5-carboxylates **80** under microwave irradiation as well as by the classical method. The beneficial effect of microwave irradiation on these reactions was a shortening of the reaction time and an increase in the yields (Scheme 13) [23].

Reaction **83** of with 4-substituted 1,3-oxazol-5(4*H*)-one **87** led to diacylhydrazines **88** or to imidazole derivatives **89** depending on the reaction temperature (Scheme 14). 1,2,4-Triazole-3-thione **91** was obtained by a two-step sequence from **83** with phenylisothiocyanate and subsequent base-catalyzed cyclization of thiosemicarbazide **90** [25].



85	R	R^1	R^2	R^3
a	Ph	H	H	H
b	Ph	H	H	Cl
c	H	H	Bn	NO_2
d	Me	H	H	Cl
e	Me	H	Bn	H
f	Me	Me	Bn	NO_2

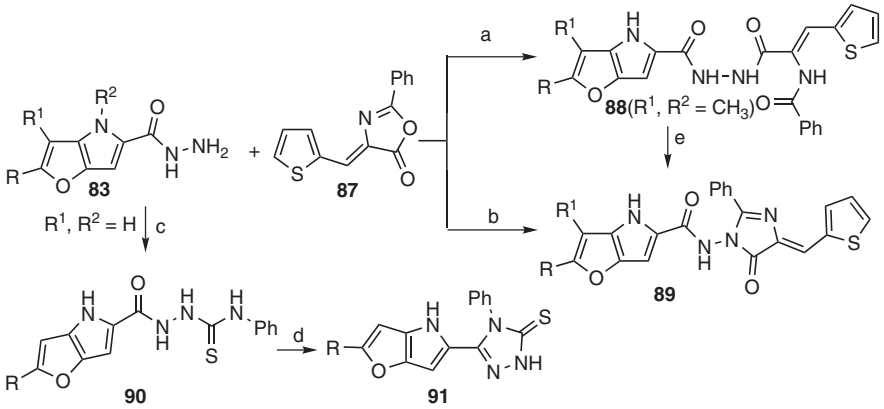
85	R	R^1	R^2	R^3
g	H	H	H	H
h	H	H	H	NO_2
i	H	H	H	Me
j	Me	Me	Me	Cl
k	CH=(CH)$_2$=CH	H		H

86	R	R^1	R^2	R^3
a	Me	Me	H	H
b	CH=(CH)$_2$=CH	H		Me

Yield (%)

	MW	Classical
86a	94	81
86b	79	77

Scheme 13 **a** 6-Substituted-4-oxochromene-3-carbaldehydes **84**, TsOH; **b** methyl 2-formyl-furo[3,2-*b*]pyrrole-5-carboxylates **80**, TsOH [24]



Scheme 14 **a** AcOH, AcOK, 80 °C, 2 h; **b** AcOH, AcOK, reflux, 2 h, or MW; **c** PhNCS, EtOH; **d** NaOH reflux; **e** EtOH reflux 1 h [25]

3 1,5-Diheteropentalene Systems

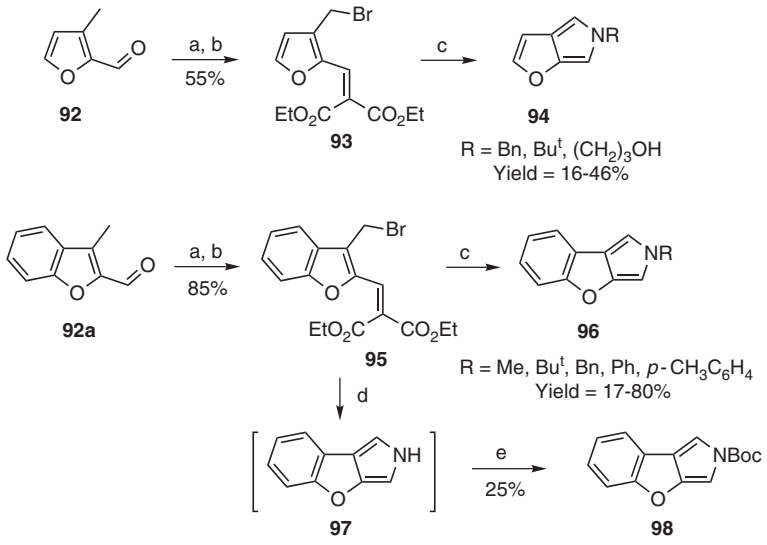
3.1 Synthesis of 1,5-Diheteropentalene Systems

The most frequent methods for the preparation of 1,5-diheteropentalene systems involve construction of the second heterocyclic ring onto an existing heterocycle. Three new syntheses of *iso*-condensed heteroaromatic pyrroles and their derivatives

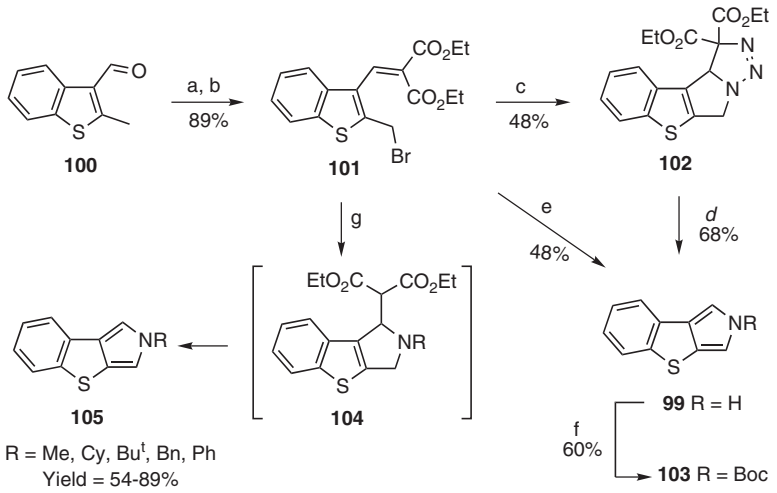
have been described [26, 27] using retro-malonate addition and/or 1,3-dipolar cycloaddition–cycloreversion methods.

Knoevenagel condensation of the corresponding 3-methylfuran-2-carbaldehyde **92** and 3-methybenzo[*b*]furan-2-carbaldehyde **92a** with diethyl malonate, followed by bromination with NBS in the presence of dibenzoyl peroxide, afforded bromides **93** and **95**, respectively. Treatment of **93** and **95** with benzylamine, isopropylamine, *t*-butylamine, 3-hydroxypropylamine, aniline, and *p*-toluidine in ethanol yielded furo[2,3-*c*]pyrroles **94** and benzo[4,5]furo[2,3-*c*]pyrroles **96**, respectively (Scheme 15). The yields of furopyrroles **94** are only moderate (16–46%) because these compounds are highly sensitive to acid, and partially polymerized upon silica gel chromatography. In addition, treatment of **95** with ammonia in ethanol gave parent compound **97**, which was not isolable, but was treated immediately with Boc_2O and DMAP to give the stable derivative **98** [26].

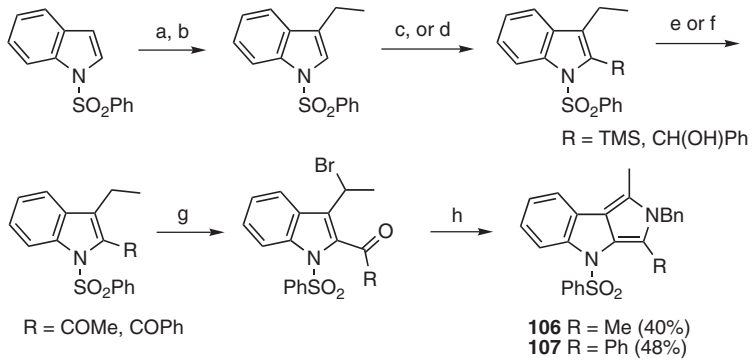
The first synthesis of the parent compound of the benzo[4,5]thieno[2,3-*c*]pyrrole ring system **99** [27] and its derivatives was accomplished using the same synthetic sequence (Scheme 16). Starting with 2-methylbenzo[*b*]thiophene-3-carbaldehyde **100**, an intermediate **101** was obtained. Treatment of bromo compound **101** with sodium azide in ethanol led to the stable triazoline **102**. 1,3-Dipolar cycloreversion of **102** was induced by a catalytic amount of *p*-TsOH to give the parent 2*H*-benzo [4,5]thieno[2,3-*c*]pyrrole **99**. Alternatively, direct treatment of bromo compound **101** with excess ammonia furnished **99** in one step. Compound **99** was treated with Boc_2O and DMAP to give the *N*-Boc derivative **103**. Reaction of **101** with alkyl- and arylamines, respectively, afforded the N-substituted benzo[4,5]thieno[2,3-*c*]pyrroles **105** via a retro-malonate addition from intermediate **104**.



Scheme 15 **a** $CH_2(CO_2Et)_2$, piperidine; **b** NBS, $(PhCO)_2O_2$; **c** RNH_2, EtOH; **d** NH_3, EtOH; **e** Boc_2O, DMAP, CH_2Cl_2 [26]



Scheme 16 **a** $CH_2(CO_2Et)_2$, piperidine; **b** NBS, $(PhCO)_2O_2$; **c** NaN_3, EtOH; **d** TsOH; **e** NH_3; **f** Boc_2O, DMAP, CH_2Cl_2; **g** three equiv. RNH_2 [27]

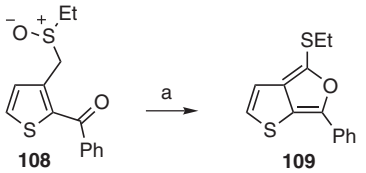


Scheme 17 **a** Ac_2O, $AlCl_3$; **b** $NaBH_4$, TFA, 94% over two steps; **c***s*-BuLi, THF, −78 °C, TMSCl, 56%; **d** PhCHO, 63%; **e** Ac_2O, $AlCl_3$, 66%; **f** MnO_2, DCM, reflux, 75%; **g** NBS, AIBN, CCl_4, 66% (R = COMe), 61% (R = COPh); **h** $BnNH_2$, K_2CO_3, $CHCl_3$ [28–30]

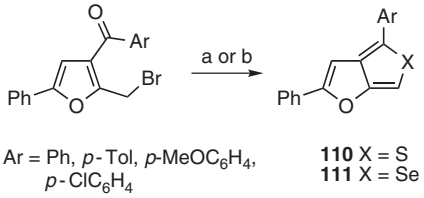
Similarly, pyrrolo[3,4-*b*]indoles **106** and **107** were synthesized according to the method of Srinivasan [28–30]. The pyrrolo[3,4-*b*]indole skeleton was obtained by cyclization of suitable precursors with bromo and carbonyl functions with benzylamine. The syntheses starting with an *N*-phenylsulfonyl-protected indole are depicted in Scheme 17.

Cyclization of suitably a substituted sulfoxide thiophene **108** in acidic conditions is the key reaction in the synthesis of 4-(ethylsulfanyl)-6-phenylthieno[2,3-*c*]furan **109** from 3-methylthiophene-2-carboxylic acid (Scheme 18) [31].

The series of new 4-aryl-2-phenylthieno[3,4-*b*]furans **110** and the selenium analog **111** were prepared from the readily available aryl 2-bromomethyl-5-phenyl-3-furyl



Scheme 18 **a** Ac_2O, *p*-TsOH, 79% [31] **108** **109**



Ar = Ph, *p*-Tol, *p*-$MeOC_6H_4$, *p*-ClC_6H_4

110 X = S
111 X = Se

Ar	X	Yield
Ph	S	75%
p-Tol	S	45%
p-$MeOC_6H_4$	S	60%
p-ClC_6H_4	S	73%
p-$MeOC_6H_4$	Se	30%

Scheme 19 **a** CH_3CSNH_2, EtOH, reflux; **b** $EtCSeN(Et)_2$, EtOH, reflux [32]

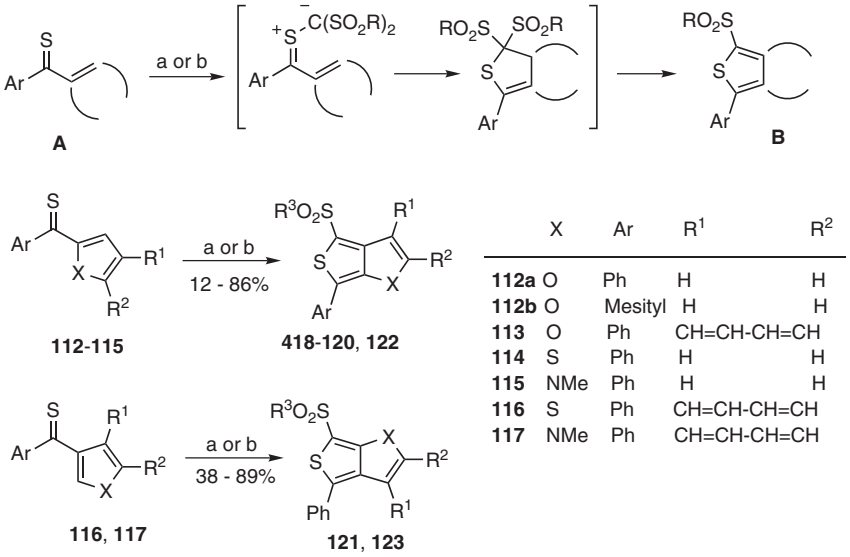
ketones by cyclization with thioacetamide and *N*,*N*-diethylselenopropanamide, respectively (Scheme 19) [32].

Saito et al. [33] described a new method for the synthesis of heterocycle-fused[*c*]thiophenes via reaction of aryl heteroaryl thioketones with carbene precursors. Heteroaromatic thioketones **A** react with carbenoids generated from bis(arylsulfon yl)diazomethanes or phenyliodonium bis(phenylsulfonyl)methylides to give heterocycle-fused[*c*]thiophenes **B** (Scheme 20). The reaction involves the ring closure of the intermediary thiocarbonyl ylides, followed by restorative aromatization via the elimination of a sulfenic acid. The present method provides simple and facile access to a variety of furo- **118**, benzofuro- **119**, thieno- **120**, benzothieno- **121**, pyrrolo- **122**, and indolo- **123** fused [*c*]thiophenes (Scheme 20).

The fused heterocycle 4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole **126**, which is an indole-2,3-quinodimethane synthetic analog, was prepared in five steps from indole in 48% overall yield [34]. Indole-3-carbaldehyde was protected using a phase transfer method to give the *N*-phenylsulfonyl derivative **124** (Scheme 21). Acetalization under typical conditions gave the acetal in excellent yield. Lithiation of the acetal at C-2 with *sec*-BuLi followed by treatment with gaseous formaldehyde gave hydroxy acetal **125**, which was treated without isolation with $BF_3{\cdot}Et_2O$ and hydroquinone to afford furoindole **126** in 52% yield from the acetal. This sequence was used to synthesize C-3 alkyl derivatives using the corresponding aldehydes for hydroxyalkylation (Scheme 21). Exposure of the hydroxy acetals **125** to TFA and hydroquinone in dichloromethane at room temperature afforded 3-methyl-, 3-phenyl-, and 3-heptyl furoindoles **126**. The overall yields of the 3-alkyl furoindoles **126** from indole were 46–63% [34].

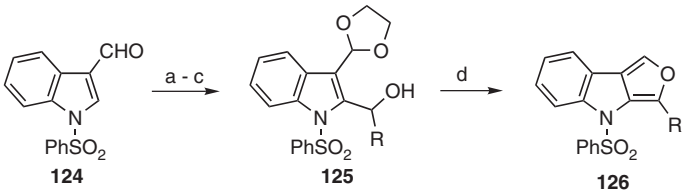
Cyclization of 3-nitroindoles **127** with ethyl isocyanoacetate and DBU (conditions of Barton–Zard pyrrole synthesis) gave the corresponding pyrrolo[3,4-*b*]indoles **128** (Scheme 22) [35].

A tandem of intramolecular Diels–Alder/retro-Diels–Alder reaction sequences were applied in the syntheses of many A,B-diheteropentalenes [2]. Gribble and coworkers

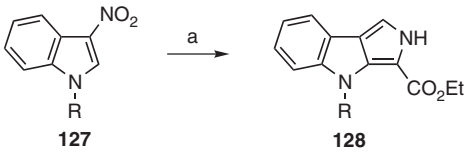


	X	Ar	R^1	R^2
112a	O	Ph	H	H
112b	O	Mesityl	H	H
113	O	Ph	CH=CH-CH=CH	
114	S	Ph	H	H
115	NMe	Ph	H	H
116	S	Ph	CH=CH-CH=CH	
117	NMe	Ph	CH=CH-CH=CH	

Scheme 20 **a** $N_2C(SO_2R^3)_2$, $Cu(acac)_2$, toluene, reflux, 5 min – 1 day; **b** Ph^+ $IC^-(SO_2Ph)_2$, $Cu(OAc)_2$, toluene, reflux, 0.5–1 h [33]

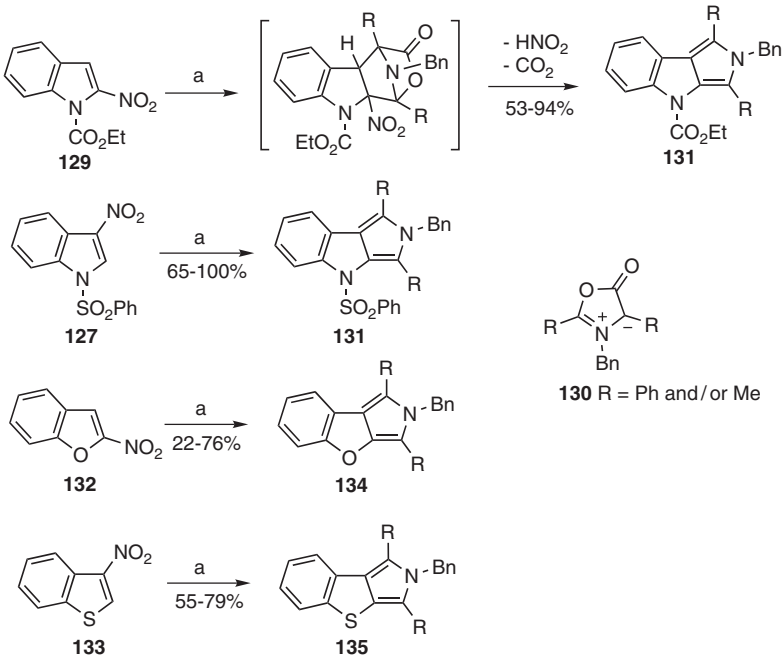


Scheme 21 **a** $(CH_2OH)_2$, *p*-TsOH, benzene, 97%; **b***s*-BuLi, THF, −78 °C; **c** RCOH; **d** $BF_3{\cdot}Et_2O$, THF, hydroquinone or TFA, CH_2Cl_2, hydroquinone, R = H (52%), Me (52%), Ph (61%), *n*-C_7H_{15} (70%), yields over last three steps [34]



Scheme 22 **a** $CNCH_2CO_2Et$, DBU, THF, R = CO_2Et (91%), R = CO_2Bu^i (80%), R = CO_2Bu^t (90%) [35]

[29] reported new syntheses of pyrrolo[3,4-*b*]indoles **131**, benzo[4,5]furo[2,3-*c*]pyrroles **134**, and benzo[4,5]thieno[2,3-*c*]pyrroles **135** using the 1,3-dipolar cycloaddition reaction of symmetrical and/or unsymmetrical [30] münchnones (1,3-oxazolium-5-olates) with nitroheterocycles. Both 2- and 3-nitroindoles react with mesoionic münchnones

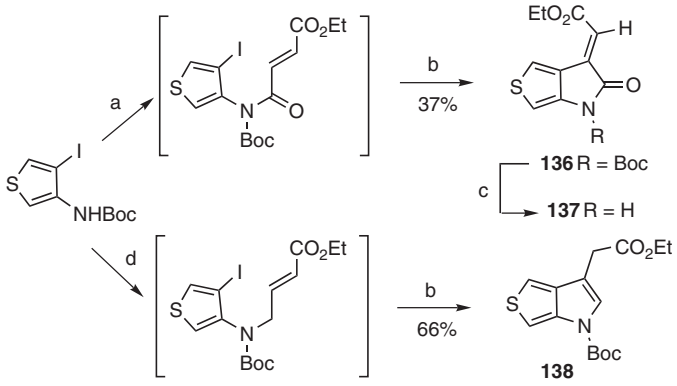


Scheme 23 **a** Münchnone **130**, THF, heat [29, 30]

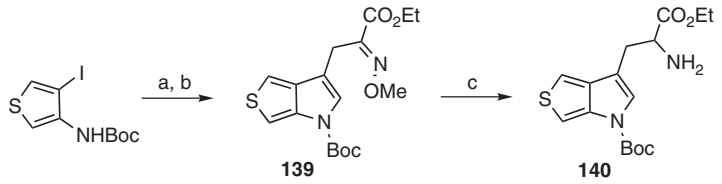
130 to give in one operation the corresponding pyrrolo[3,4-*b*]indoles **131**. This reaction is presumed to involve the formation of a cycloadduct that loses the elements of nitrous acid and carbon dioxide to afford the pyrrolo[3,4-*b*]indole **131** in good to excellent yield (Scheme 23). Likewise, both 2-nitrobenzo[*b*]furan **132** and 3-nitrobenzo[*b*]thiophene **133** give rise to the novel fused heterocycles **134** and **135**, respectively.

Gronowitz et al. [30] reported synthesis of indole-3-acetic acids and hetero analogs using an intramolecular Heck reaction. 1-Boc-(*E*)-3-(ethoxycarbonylmethylene)-2-oxo-2,3-dihydrothieno[3,4-*b*]pyrrole **136** and ethyl 1-Boc-thieno[3,4-*b*]pyrrol-2-ylacetate **138** were prepared starting from *N*-Boc-protected 3-amino-4-iodothiophene. Acylation with ethyl 4-bromocrotonate and ethyl fumaroyl chloride, respectively, followed by palladium-catalyzed ring closure in a one-pot reaction, yielded the *N*-Boc-protected thieno[3,4-*b*]pyrroles **136** and **138**, respectively. The Boc-group of **136** was readily removed after adsorption on silica to yield **137** (Scheme 24).

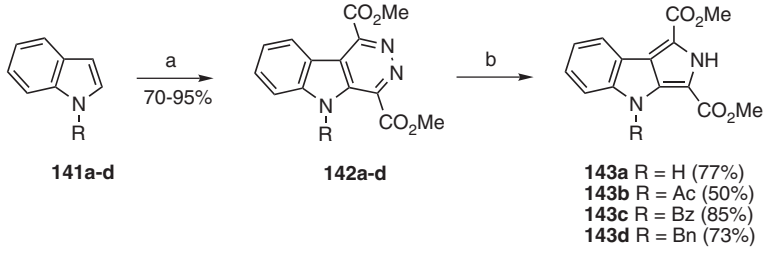
This synthetic route was applied in the synthesis of thia-tryptophans, which are of interest as potentially bioactive molecules [36]. 5,6-Thia-(d,l)-tryptophan ethyl ester **140**, with an additional Boc protecting group attached to nitrogen due to the instability of the parent ring system, was prepared from the corresponding 3-Boc-amino-4-iodothiophene using a one-pot synthesis including Heck cyclization [37]. Firstly, allylation of the 3-amino-4-iodothiophene derivative with ethyl (*E*)-2-[(*E,Z*)-methyloximino]-5-bromo-3-pentenoate (92:8), and subsequent Heck-type cyclization in the presence of palladium acetate afforded the desired thieno[3,4-



Scheme 24 **a** Ethyl fumaroyl chloride, NEt_3, DMAP, THF; **b** $Pd(OAc)_2$, PPh_3, THF, 37%; **c** silica gel, 1 mmHg, 50 °C, 87%; **d** 4-bromocrotonate, K_2CO_3, DMF [30]



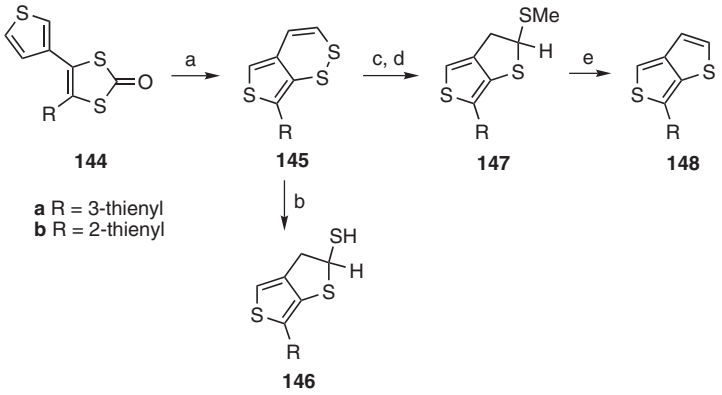
Scheme 25 **a** Ethyl (*E*)-2-[(*E,Z*)-methyloximino]-5-bromo-3-pentenoate, Cs_2CO_3, DMF; **b** $Pd(OAc)_2$, PPh_3, K_2CO_3, 60–65 °C, 58% over two steps; **c** Al (Hg), wet THF, 86% [37]



Scheme 26 **a** Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate; **b** Zn, AcOH [38]

b]pyrrole **139**. Reduction of the oxime ether function in **139** using Al(Hg) in wet THF provided the target *N*-Boc-protected thia-tryptophan **140** (Scheme 25).

A facile preparation of pyrrolo[3,4-*b*]indoles **143** from pyridazino[4,5-*b*]indoles **142** using a Zn/AcOH reductive ring contraction has been described [38]. Since compounds **142** are easily prepared from the inverse electron demand cycloaddition of indoles **141** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, this represents a simple, two-step sequence to prepare the pyrroloindoles **143** (Scheme 26).



Scheme 27 **a** hν, 6 h, **145a** (76%), **145b** (76%); **b** $NaBH_4$, EtOH, **146a** (65%), **146b** (78%); **c** $NaBH_4$, EtOH; **d** MeI, Na_2CO_3, RT, **147a** (69% from **144a**), **147b** (71% from **144b**); **e** MeI, heat, **148a** (72%), **148b** (66%) [39]

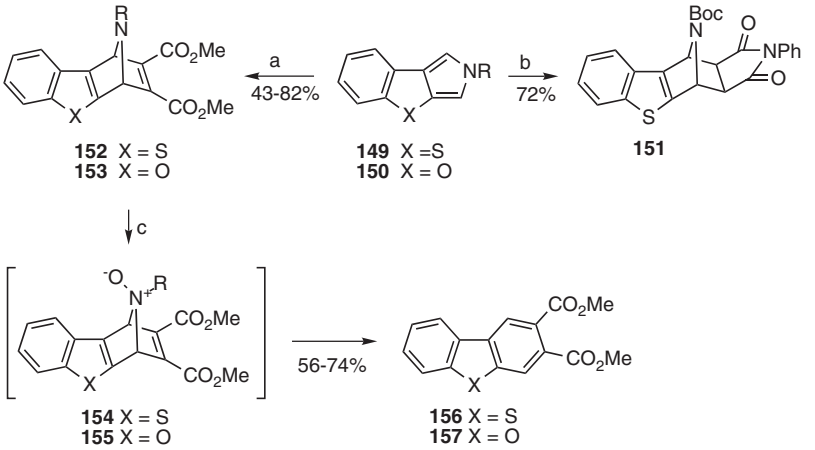
Reductive ring contraction of the 1,2-dithiine skeleton was applied in the formation of the thiophene ring. Thieno[3,4-*b*]thiophenes **148** were prepared from thiophen-3-yl-substituted [1,3]dithiol-2-ones **144** in good yields [39]. The photochemical irradiation of **144** leads to thieno[3,4-*c*]dithiines **145** via a unique ring cleavage reaction, and subsequent reductive treatment of dithiines **145** proceeds to give 2,3-dihydrothieno[3,4-*b*]thiophenes **146** and **147**. Heating of **147** in the presence of further iodomethane leads to the formation of the thieno[3,4-*b*]thiophenes **148** (Scheme 27).

3.2 Reactions of 1,5-Diheteropentalene Systems

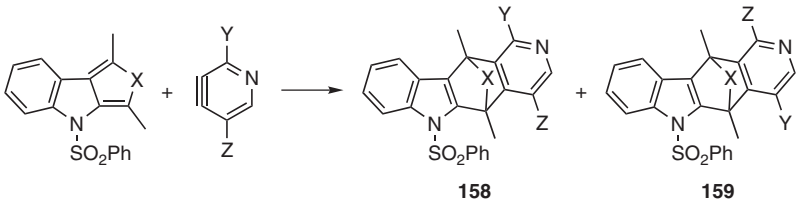
These 10π-systems are isoelectronic with the pentalene dianion and have been of some theoretical interest. 1,5-Diheteropentalene systems are very popular substrates for the investigation of inter- and intramolecular cycloaddition reactions due to their diene character. Such cycloaddition processes allow for a rapid entry into complex polyheterocyclic rings and makes these compounds potentially useful for natural product synthesis.

Diels–Alder reactions of N-substituted benzo[4,5]thieno[2,3-*c*]pyrroles **149** [27] and benzo[4,5]furo[2,3-*c*]pyrroles **150** [26] with *N*-phenylmaleimide and DMAD gave the corresponding *exo* cycloadducts **151–153** (Scheme 28). Oxidative extrusion of the nitrogen bridge in cycloadducts **152** and **153** via intermediates **154**, **155** afforded derivatives of dibenzothiophene **156** [27] and dibenzofuran **157** [26].

The regioselectivity of 2,4-cycloaddition of furo- and pyrrolo[3,4-*b*]indoles with 3,4-didehydropyridines was studied [40]. The results of this key reaction step in the synthesis of ellipticines **158**, **159** are summarized in Scheme 29.



Scheme 28 **a** DMAD, Et_2O, reflux, 12 h (for **149**) or DMAD, benzene, RT, 12 h (**150**); **b** NPMI, benzene, reflux, 3 h; **c** MCPBA, DCM, RT, 30 min [26, 27]

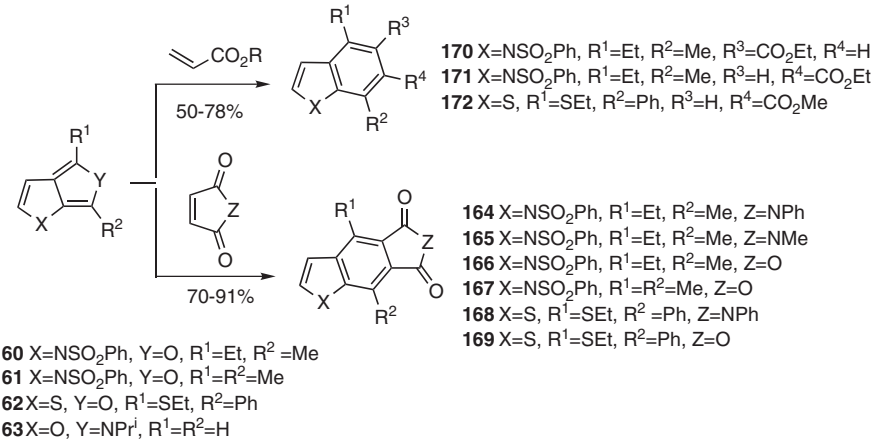


X	Y	Z	Yield	Ratio **158**:**159**
O	Cl	H	88%	2.4:1
O	Br	H	40%	1:1
O	F	H	38%	1.1:1
O	H	F	64%	1:1
NH	Cl	H	44%	1.7:1
NH	Br	H	28%	1:1
NBoc	Cl	H	52%	1:1

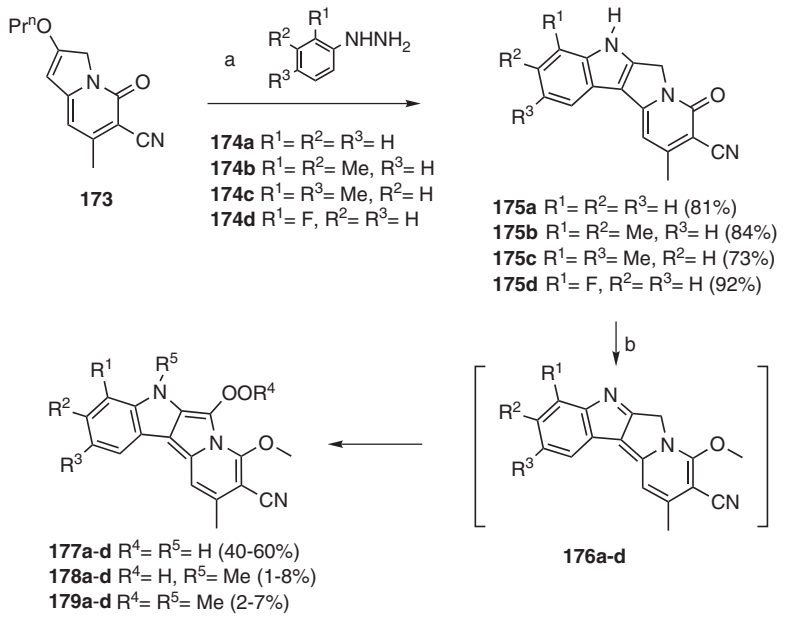
Scheme 29 Regioselectivity of 2,4-cycloaddition of furo- and pyrrolo[3,4-*b*]indoles with 3,4-didehydropyridines [40]

The furo[3,4-*b*]pyrroles **160**, **161** [41], thieno[2,3-*c*]furan **162**, [31] and furo [2,3-*c*]pyrrole **163** [26], which are mostly less stable than the benzo-fused analogs, were trapped by Diels–Alder reactions with dienophiles followed by elimination of water to give the corresponding indoles **164**–**167, 170**, and benzothiephenes **168**, **169**, and **172** with good to excellent yields (Scheme 30).

The new tetracyclic 9*H*,10*H*-indolizino[1,2-*b*]indol-1-one derivatives **175a–d** have been synthesized by modified Fischer indole synthesis from the enol ether **173** of 2,5-dihydroxy-7-methyl-6-cyano-indolizineand arylhydrazines **174a–d** (Scheme 31) [42]. Attempted N-methylation of **175a–d** produced a series of autoxidized products including 10-hydroperoxy-1-methoxyindolizino[1,2-*b*]indole **177a–d** as the major product, accompanied by methylperoxides **178a–d** and **179a–d** as the minor products.



Scheme 30 Formation of indoles **164**–**167, 170, 171** and benzothiephenes **168**, **169**, and **172** from **160**–**163** [41]



Scheme 31 **a** $ArNHNH_2$, AcOH, HCl, reflux, 3 h; **b** MeI, K_2CO_3, or Me_2SO_4, $KOBu^t$ [42]

A plausible mechanism for the autooxidation is postulated based on the isolation of some intermediates. The reaction is thought to proceed through intermediates **176a–d** followed by a novel type of autooxidation. The first step involves abstraction of the indole NH proton in **175** and subsequent O-methylation to form azaenolate derivatives **176**, which tautomerize to the enamines. The second step, autooxidation, is thought to be a free-radical process.

4 1,6-Diheteropentalene Systems

4.1 Synthesis of 1,6-Diheteropentalene Systems

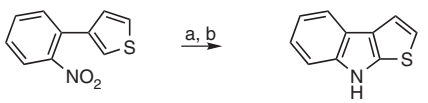
4.1.1 Synthesis by Construction of the Second Heterocyclic Ring onto the Existing Heterocycle

The 8*H*-thieno[2,3-*b*]indole **181** was prepared from 3-(2-nitrophenyl)thiophene **180** by a palladium-catalyzed regioselective C–H bond functionalization driven by CO as the stochiometric reductant. The compound **181** was obtained as a mixture of regioisomers in the ratio 93:7, determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. After flash chromatography, **181** was isolated as a major isomer in 81% yield [43] (Scheme 32).

The 8*H*-thieno[2,3-*b*]indole **181** was prepared a by tandem of cross-coupling and cyclization reactions in very good yield (76%) [13] from 2-nitroboronic acid **25** and 3-bromothiophene **182** (Scheme 33) analogously to 4*H*-thieno[3,2-*b*]indole **28** (see Scheme 33).

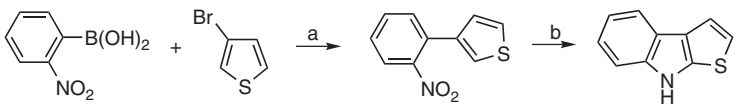
The total synthesis of alkaloid thienodolin **185a** and its 5-chloro isomer **185b** as well as its unsubstituted analog **185c** was published by Bergman and coworkers [44] starting from the appropriate 2-chloroindole-3-carbaldehydes **183a–c** via intermediates **184a–c** in total yields of 42%, 35%, and 37%, respectively (Scheme 34). The alkaloid **185a** was isolated from the culture broth of *Streptomyces albogriseolus* MJ286-76F7 and structurally elucidated by Nakamura et al. [45]. The alkaloid **185a** was shown to exhibit both growth promoting and inhibiting activities in rice seedlings.

1-(Thieno[2,3-*b*]thiophen-3-ylmethyl)-1*H*-[1,2,3]benzotriazole **189** and (benzo[4,5]thieno[2,3-*b*]thiophen-3-ylmethyl)-1*H*-[1,2,3]benzotriazole **190** were readily available from the condensation of 1-(1*H*-[1,2,3]benzotriazol-3-yl)-3-chloroacetone **186** with corresponding thiols via intermediate sulfides **187**, **188**. Reaction of



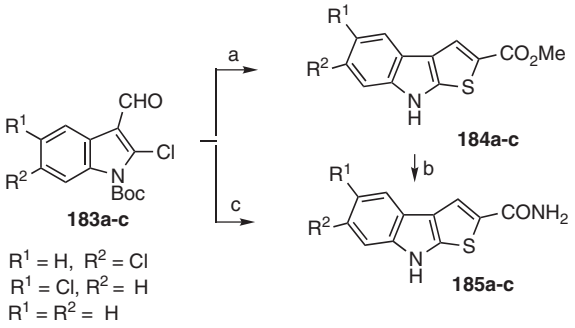
180 182

Scheme 32 **a** 2 mol% of $Pd(OAc)_2$, 4 mol% of 1,10-phenatroline, 70 psig of CO, 140 °C, DMF, 16 h; **b** flash chromatography [43]

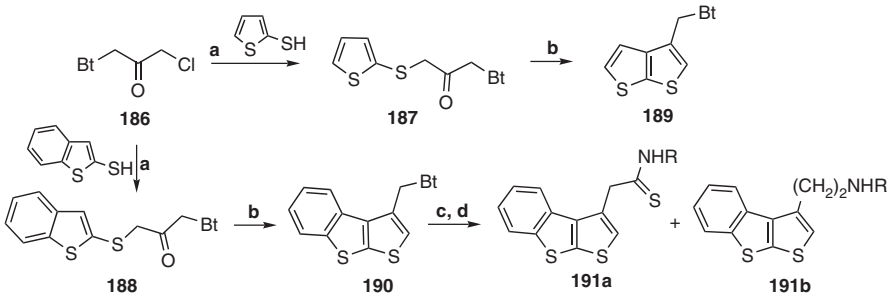


25 182 180 181

Scheme 33 **a** $Pd(Ph_3P)_4$, $NaHCO_3$, DMF–H_2O (1:1), MW, 15 min; **b** $(EtO)_3P$, MW, 15 min [13]



Scheme 34 **a** Methyl thioglycolate, reflux, 16 h; **b** ammonia, methanol, sealed tube, 80 °C, 6 days; **c** 2-sulfanyl acetamide, methanol, reflux, 16 h [44]



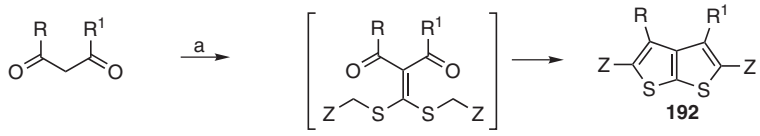
Scheme 35 **a** KOH, EtOH/H_2O, reflux; **b** $ZnCl_2$, benzene, reflux; **c** BuLi, −78 °C, then RNCS; **d** Zn/AcOH [46]

190 with BuLi and 1-naphthyl isothiocyanate followed by reduction with Zn–AcOH led to formation of thioamide **191a** (53%) and amine **191b** (27%) (Scheme 35) [46].

4.1.2 Synthesis from Acyclic Precursors

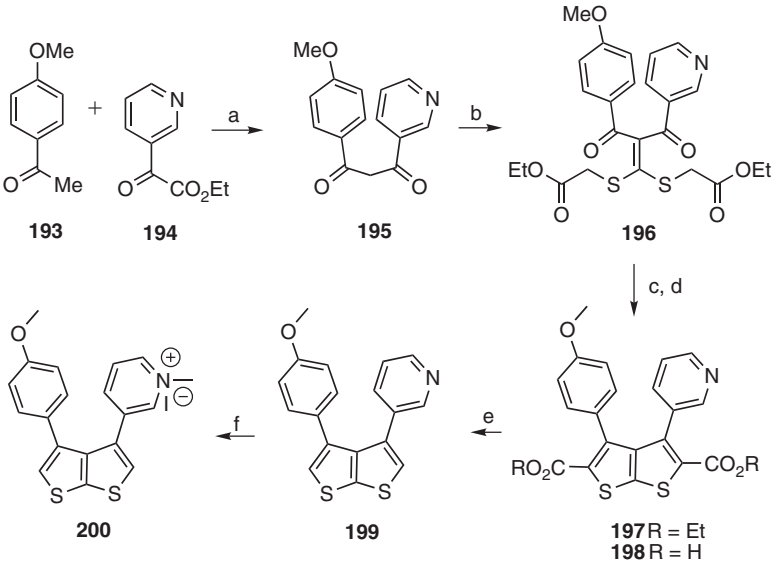
A simple one-pot synthesis of tetrasubstituted thieno[2,3-*b*]thiophenes **192** by condensation 1,3-diketones with CS_2, and alkylating agents carrying an EWG such as CO_2Et, COR, or CN in the presence of anhydrous KF as condensation promoter in anhydrous DMF was described (Scheme 36) [47, 48]. The authors examined several other solvents such as anhydrous dioxane, THF, or MeCN, but they were found to be ineffective.

The above method was used for preparation of a new class of cofacially oriented neutral donor–acceptor thienothiophenes, namely 3-(4-methoxyphenyl)-4-(3-pyridyl) thieno[2,3-*b*]thiophene **199** and its ionic analog **200** (Scheme 37). The synthesis of **199** and **200** has been described to probe the presence of through-space charge transfer interactions [49].



192a R = R^1 = Me, Z = CO_2Et (50%) **192e** R = R^1 = Ph, Z = COMe (67%)
192b R = R^1 = Me, Z = COMe (46%) **192f** R = R^1 = 4-MeC_6H_4, Z = CO_2Et, (61%)
192c R = R^1 = Me, Z = COPh (40%) **192a** R = R$_1$ = 4-MeC_6H_4, Z = COMe (36%)
192d R = R^1 = Ph, Z = CN (67%)

Scheme 36 **a** CS_2, X–CH_2–Z, KF, DMF, R, R^1 Me, Ph, *p*-Tol, $MeOC_6H_4$; X: Cl, Br; Z, CO_2Et, COMe, COPh, CN [47, 48]

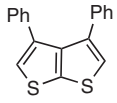


Scheme 37 **a** NaH/DMF, 0 °C-RT 6 h, 66%; **b** CS_2, Na_2CO_3, RT, 1 h, then $BrCH_2CO_2Et$, RT, 24 h, 60%; **c** EtONa/EtOH, 0 °C, 1 h, 50%; **d** DMSO, KOH, 100 °C, 10 h, then H^+, 85%; **e** 240–250 °C, 10 min, N_2, 32%; **f** MeI/MeCN, RT, 48 h, 100% [49]

1-(4-Methoxyphenyl)-3-pyridine-3-ylpropane-1,3-dione **195** was prepared by condensing 4-methoxyacetophenone **193** with ethyl nicotinate **194** using sodium hydride as the base. The reaction **195** with CS_2 and anhydrous K_2CO_3 in DMF, followed by treatment with two equivalents of ethyl bromoacetate, provided ketene dithioacetal **196** as an oil. The treatment of **196** with sodium ethoxide in absolute ethanol led to spontaneous cyclization to afford the expected diethyl 3-(4-methoxyphenyl)-4-(pyridin-3-yl)thieno[3,2-*b*]thiophene-2,5-dicarboxylate **197**. The hydrolysis of **197** with KOH in aqueous DMSO gave upon acidification the dicarboxylic acid **198**, which by thermal decarboxylation followed by SiO_2

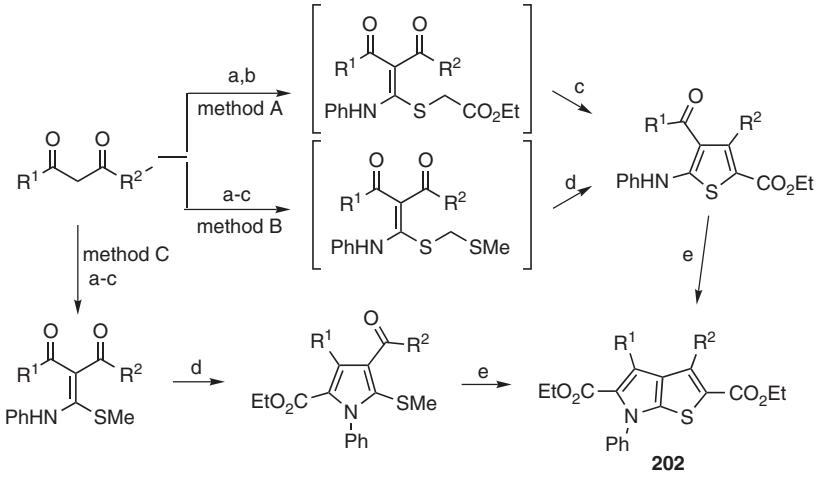
chromatographic purification afforded **199**. To enhance the acceptor character of the pyridyl ring, the compound **199** was quaternized with MeI to obtain the *N*-methyl pyridinium salt **200**. However, structural analysis by high resolution ^{1}H NMR and UV–visible absorption spectra revealed rather weak through-bond charge transfer interaction in **200**. An X-ray crystal structure of **200** revealed key structural features that work against appreciable through-space charge transfer interaction. Conformational analysis of a model system, 3,4-diphenylthieno[2,3-*b*]thiophene **201** (Fig.12), indicated that conformations with reduced torsion between the phenyl rings and the thieno[2,3-*b*]thiophene plane are possible to maintain a balance between conjugation and steric congestion. The calculated low energy barrier between the high and low energy conformations of the model system suggests the possibility of aryl ring rotations in *peri* disubstituted thieno[2,3-*b*]thiophenes [49].

Thieno[2,3-*b*]pyrrole derivatives **202** were easily synthesized in different ways using phenyl isothiocyanate and activated methylene compounds (Scheme 38) [50–53]. The priority of the thiophene or pyrrole ring formation was investigated. The authors have shown that, except for some rare cases, the best way to prepare thieno[2,3-*b*]pyrrole derivatives **202** is the formation of appropriate thiophenes, in one or two steps, prior to the pyrrole.



201

Fig. 12 3,4-Diphenyl thieno[2,3-*b*]thiophene **201** [49]

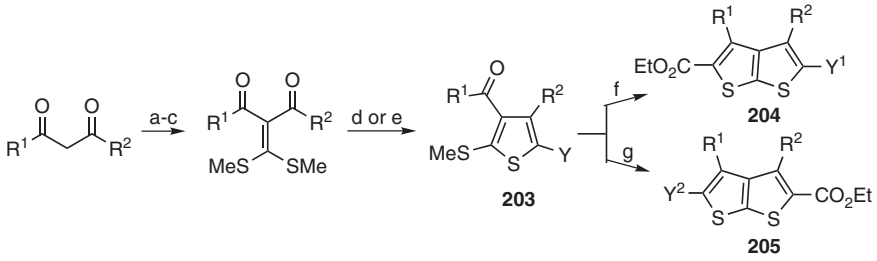


202

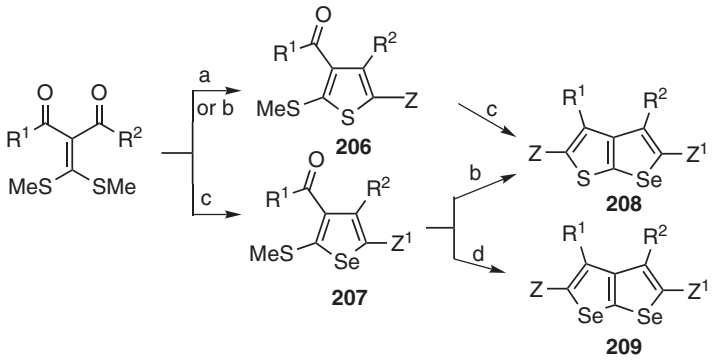
Scheme 38 *Method A*: **a** K_2CO_3, DMF; **b** PhNCS; **c** $BrCH_2CO_2Et$, K_2CO_3, DMF; **d** $BrCH_2CO_2Et$, K_2CO_3, acetone. *Method B*: **a** K_2CO_3, DMF; **b** PhNCS; **c** MeI; **d** $HSCH_2CO_2Et$, K_2CO_3, EtOH; **e** $BrCH_2CO_2Et$, K_2CO_3, acetone. *Method C*: **a** K_2CO_3, DMF; **b** PhNCS; **c** MeI; **d** $BrCH_2CO_2Et$, K_2CO_3, acetone; **e** $HSCH_2CO_2Et$, K_2CO_3, EtOH [50–53]

Two different ways leading to asymmetrically substituted thieno[2,3-*b*]thiophenes **204**, **205** have been described (Scheme 39) [54]. The first one is based on the reaction of thiophenes **203**, obtained from ketene dimethylthioacetals and an appropriate halogen derivative in the presence of sodium sulfide, with ethyl thioglycolate and potassium carbonate as the reaction promoters. In the second method, ethyl thioglycolate and the halogen derivative with sodium sulfide were exchanged in two steps of this synthetic path. The authors [54] stated that they preferred, for practical reasons, the second method giving the higher yields.

The synthesis of substituted selenolo[2,3-*b*]thiophenes **208** and selenolo [2,3-*b*] selenophenes **209** via ketene dithioacetals has been published (Scheme 40) [55]. The easy access to ketene dithioacetals via carbon disulfide cannot be applied to selenium since the strongly odorous carbon diselenide cannot be readily prepared. The authors [55] overcame this problem using sodium selenide for the synthesis of selenolo[2,3-*b*]thiophenes **208**, which could be synthesized from methylsulfanylthiophenes **206** and sodium selenide and/or from 5-methylsulfanylselenophenes **207** and thioglycolate.



Scheme 39 **a** K_2CO_3, DMF, RT; **b** CS_2; **c** MeI; **d** Na_2S, XCH_2Y^1, K_2CO_3, DMF, RT; **e** $HSCH_2Y$, K_2CO_3, RT; **f** $HSCH_2CO_2Et$; **g** for $Y^1 = CO_2Et$, Na_2S, XCH_2Y^2, $Y^1 = CO_2Et$, COPh, COMe; Y^2 = CHO, COPh, COMe, CN [54]



Scheme 40 **a** Na_2S, X–CH_2–Z; **b** HS–CH_2–CO_2Et; **c** Na_2Se, X–CH_2–Z^1; **d** Na_2Se, X–CH_2–Z [55]

Recently, the synthesis of 5-aryl-2-oxopyrrole derivative **210** as synthon for the highly substituted pyrrole **211** as starting compound for fused heterocycle **212** was published [56]. Diethyl 6-benzyl-5-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,4-dicarboxylate **212** was prepared from ethyl 1-benzyl-5-chloro-4-formyl-2-phenyl-1*H*-pyrrole-3-carboxylate **211** and ethyl 2-sulfanylacetate in refluxing ethanol (Scheme 41).

4.2 Reactions of 1,6-Diheteropentalene Systems

4.2.1 Electrophilic Attack at Carbon

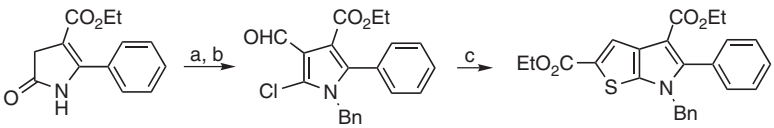
The Vilsmeier formylation of methyl furo[2,3-*b*]pyrrole-5-carboxylate **213a** and its variously N-substituted derivatives **213b–d** has been studied and **214a–d** obtained (Scheme 42) [57, 58].

4.2.2 Enzyme-Catalyzed Attack at Carbon

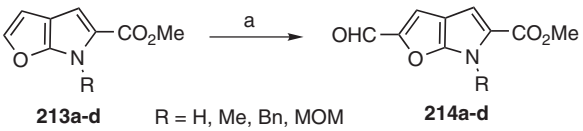
4-(6*H*-Thieno[2,3-*b*]pyrrolyl)-l-alanine **217** and 4-(6*H*-selenolo[2,3-*b*]pyrrolyl)-l-alanine **218**, have been synthesized via reactions of thieno[2,3-*b*]pyrrole **215** and selenolo[2,3-*b*]pyrrole **216**, respectively, with l-serine (Scheme 43). The reactions are catalyzed by *Salmonella typhimurium* tryptophan synthase [59,60].

4.2.3 Electrophilic Attack at Nitrogen

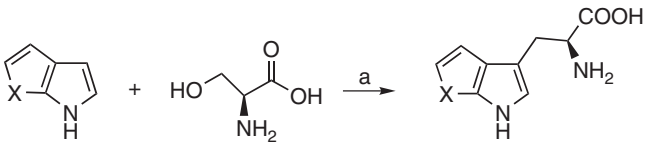
Compounds **213c,d** were obtained by direct substitution of the in-situ prepared sodium salt of **213a** in DMF (Scheme 44). This method was more efficient



Scheme 41 **a** $POCl_3$, DMF, 100–120 °C; **b** BnBr, K_2CO_3, MeCN 60 °C, 24 h; **c** ethyl 2-sulfanyl acetate, K_2CO_3, EtOH, reflux [56]



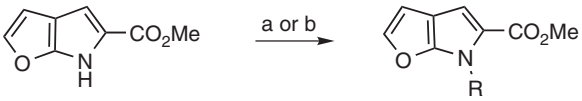
Scheme 42 **a** $POCl_3$, DMF [57, 58]



215 X = S
216 X = Se

217 X = S
218 X = Se

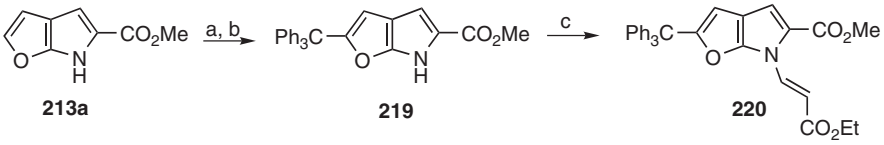
Scheme 43 **a** Tryptophan synthase [59, 60]



213a

213c R = Bn
213d R = MOM

Scheme 44 **a** RX, benzyltriethyl ammonium chloride, NaOH; **b** (i) NaH, DMF; (ii) RX, X = Cl or Br [57, 61]



213a **219** **220**

Scheme 45 **a** NaH, DMF; **b** Ph_3CCl; **c** ethyl propionate, MeCN [47]

[61] than the preparation of **213b,c** from **213a** under phase transfer catalysis conditions [57].

An attempt to introduce a triphenylmethyl bulky substituent in N-6 position of methyl 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate **213a** led to C-2 triphenylmethyl substitution giving the product **219**, which with ethyl propionate in acetonitrile gave the Michael addition product **220** [47] (Scheme 45).

4.2.4 Addition and Cycloaddition Reactions

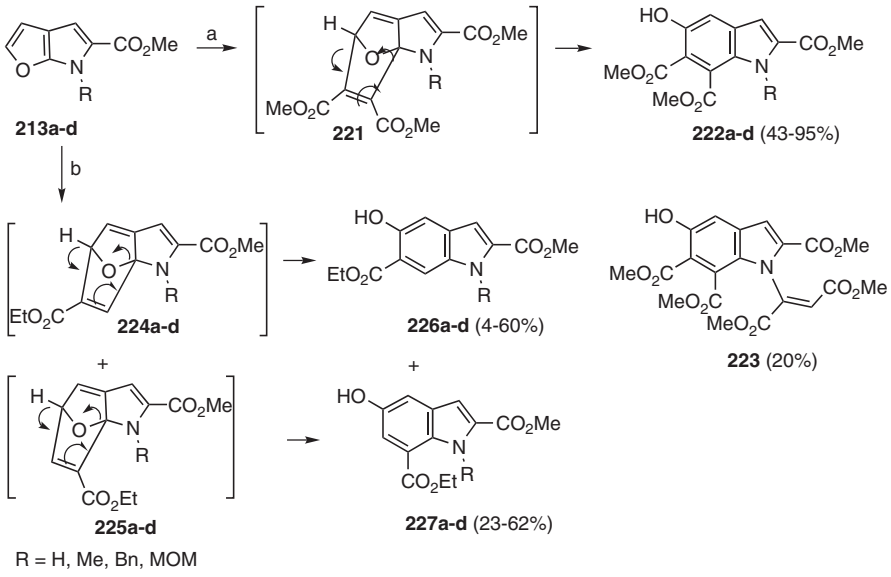
The reactions of the methyl furo[2,3-*b*]pyrrole-5-carboxylates with DMAD were described in [2, 3]. The authors [61] stated that the reactions of **213b–d** with DMAD in acetonitrile gave only cycloaddition products **222b–d** in good yields. The formed (undetected) cycloadducts **221** are obviously labile, and are transformed by opening of the furan ring into the corresponding indole derivatives **222a–d**. The reaction of methyl 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate **213a** under the same conditions gave **222a** along with a minor Michael-type addition product **223**. The reaction with ethyl propionate afforded two regioisomeric adducts **224a–d** and **225a–d**, which rearranged into minor methyl 6-ethoxycarbonyl-5-hydroxyindole-2-carboxylates **226a–d** and major 7-ethoxycarbonyl-5-hydroxyindole-2-carboxylates **227**. The ratio of the

products **226/227** is not dependent on the substituents attached in C-6 of the furo[2,3-*b*]pyrrole system (Scheme 46). Comparing the course of the Diels–Alder reactions of furo[2,3-*b*]pyrroles with their [3,2-*b*] isomers, it was stated that the [2,3-*b*] system is a more active diene than its [3,2-*b*] isomer [61].

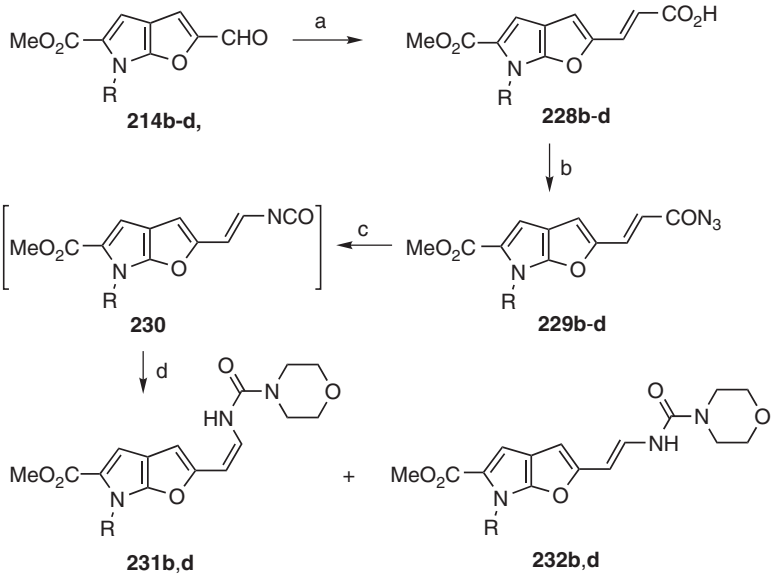
4.2.5 Reactions of Substituents Attached to 1,6-Diheteropentalene Systems

Starting from aldehydes of furo[2,3-*b*]pyrrole type **214b–d** via the Doebner condensation, the corresponding propenoic acids **228b–d** were synthesized, then reacted with ethyl chloroformate and triethylamine in acetone to give mixed acid anhydrides, which were converted to acyl azides **229b–d** with (*E*)-configuration at the double bond. The azides **229b–d** were heated in Dowtherm at 240 °C, which facilitated the Curtius rearrangement to corresponding non-isolated isocyanates **230**. The isocyanate formation was proved without their isolation in an addition reaction of **230b** and **230d** with morpholine in boiling benzene. As expected, ratio disubstituted ureas **231b** and **231d** as a mixture of (*E*) and (*Z*) isomers in 3:7 were obtained. An attempt to prepare or separate the only (*E*)-isomer was unsuccessful. If the reaction was carried out in boiling toluene, only (*Z*)-isomers of the pure new disubstituted ureas **232b** and **232d** were isolated (Scheme 47) [47].

The condensation reactions of 2-formylfuro[2,3-*b*]pyrrole-5-carboxylates **214b,d** with hippuric acid were carried out in dry acetic anhydride catalyzed by potassium acetate, providing **233b** (66%) and **233d** (70%) (Fig. 13) [22]. The reaction



Scheme 46 **a** DMAD, **b** ethyl propionate [61]



Scheme 47 **a** $CH_2(CO_2H)_2$, pyridine, piperidine; **b** (i) Et_3N, acetone; (ii) $ClCO_2Et$, NaN_3; **c** benzene, reflux; **d** morpholine [47]

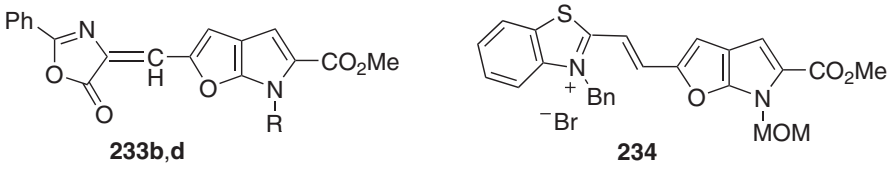


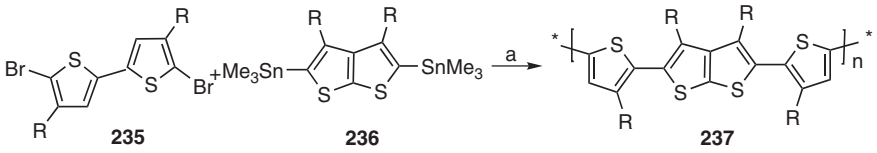
Fig. 13 6-Methyl-2-[(*E*)-(oxo-2-phenyl-1,3-oxazol-5(4*H*-ylidene)methyl]furo[2,3-*b*] pyrrole-5-carboxylate **233b**, 6-methoxymethyl-2-[(*E*)-(oxo-2-phenyl-1,3-oxazol-5(4*H*-ylidene) methyl] furo[2,3-*b*]pyrrole-5-carboxylate **233d** [22]; 3-benzyl-2-{(*E*)-2-[5-(methoxycarbonyl)-6-methoxymethylfuro[2,3-*b*]pyrrol-2-yl]vinyl}-1,3-benzotiazolium bromide **234** [23]

of **214d** with 3-methyl-1,3-benzothiazolium bromide was carried out in refluxing methanol with pyridine as catalyst giving **234d** (45%) [23].

Stable polythiophene semiconductors **237** incorporating the thieno[2,3-*b*]thiophene ring system were synthesized by Stille coupling of 5,5′-dibromo-4,4′-dialkyl-2,2′-bithiophene **235** with thieno[2,3-*b*]thiophene-2,5-diylbis(trimethystannane) **236** (Scheme 48). The polymers **237** described showed both good charge carrier mobility and stability to ambient air and light [62].

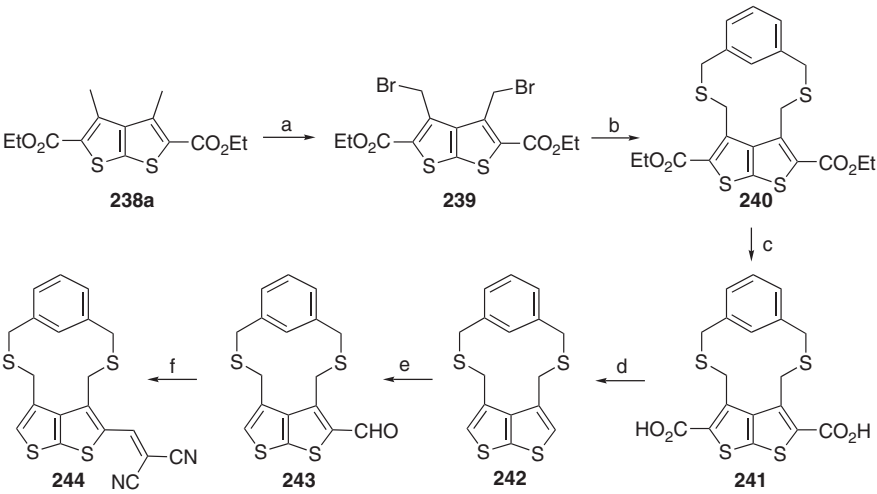
Mashraqui et al. [63] reported the synthesis of dithia-bridged cyclophanes incorporating thieno[2,3-*b*]thiophene as one of the rings, and investigated their structures and optical properties. The synthetic route affording compounds **240–244** is shown in Scheme 49.

The diethyl 3,4-dimethythieno[2,3-*b*]thiophene-2,5-dicarboxylate **238a** was readily converted into the dibromo derivative **239** (79%) by radical bromination using NBS/



235 **236** **237**

Scheme 48 **a** $Pd_2(dba)_3$/P(*o*-Tol)$_3$, MW [62]



Scheme 49 **a** NBS/CCl_4 ($PhCO_2)_2$, reflux, 1 h, 78%; **b***m*-xylylenedithiol, anhydrous K_2CO_3 in DMF, 80–90 °C, 18 h, 47%; **c** 20% KOH, ethanol, reflux, 4 h, 95%; **d** Cu, quinoline, 200 °C, 10 min, 40%; **e** DMF, $POCl_3$, 0 °C, then RT, 4 h, 57%; **f** $CH_2(CN)_2$, DMF, piperidine, 70–80 °C, 5 h, 39% [63]

dibenzoyl peroxide. High dilution coupling of **61** with *m*-xylylenedithiol in refluxing ethanol–benzene (1:1), followed by chromatographic purification over SiO_2, afforded the desired **240**. Hydrolysis of **240** gave dicarboxylic acid **241** (95%), which on decarboxylation gave the compound **242** in 40% yield. Formylation of **242** under Vilsmeier–Haack conditions provided carbaldehyde **243**, which was condensed with malononitrile (DMF/piperidine) to afford the target molecule **244** as a deep-yellow solid.

5 2,5-Diheteropentalene Systems

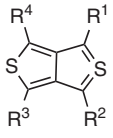
5.1 Synthesis of 2,5-Diheteropentalene Systems

The degree of π-electron stabilization exhibited within the A,B-diheteropentalenes is dependent on the relative orientation of the two heteroatoms [64, 65]. Topological resonance energy values [64] and heats of formation from MNDO calculations [65]

suggest that the heterocycles with [3,4-*c*] ring fusion will be exceedingly unstable. Experimental work on the much-studied thienothiophene series confirms this prediction. The unstable parent thieno[3,4-*c*]thiophene **6** [66] and its 4,6-dimethyl- **245** [67, 68], 4,6-bis(methoxycarbonyl)- **246** [68], and 4,6-di-*tert*-butyl- **247** as well as 4,6-di-*tert*-butyl-1,3-dimethyl- **248** derivatives [69, 70] have been generated in situ and characterized by trapping with *N*-phenylmaleimide. On the other hand, 1,3,4,6-tetraphenyl- **249** [68, 71], l,3,4,6-tetrakis(alkylsulfanyl)- **250** [72–76], l,3,4,6-tetra-2-thienyl- **251** [77], l,3-dicyano-4,6-dibromo- **252**, 4,6-dibromo-1,3-bis(methoxycarbonyl)- **253**, l,3,4,6-tetrabromo- **254** [78], 1,3-dicyano-4,6- bis(methoxycarbonyl)- **255** [79], as well as 1,4-bis(*tert*-butylsulfanyl)-3,6-diphenyl- **256** and 1,4-bis(*tert*-butylsulfanyl)-3,6-di-2-thienylthieno[3,4-*c*]thienophenes **257** [80] were successfully synthesized as isolable compounds. These isolable thieno[3,4-*c*]thiophenes owe their stability to steric hindrance together with resonance and the electron-withdrawing effects of the substituents (Fig. 14).

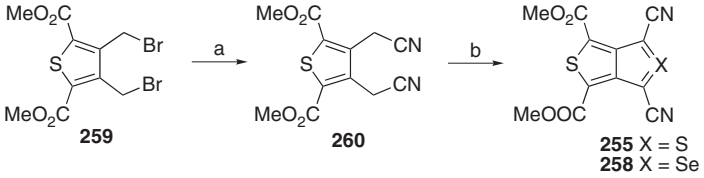
A general strategy has been to prepare 3,4-dibromomethylthiophenes bearing substituents at the 2,5-positions. Treatment with sodium sulfide led to the 1,3-dihydrothieno[3,4-*c*]thiophene derivatives, which were oxidized to the corresponding sulfoxides. The latter were subjected to a Pummerer dehydration with either acetic anhydride or base to give the target thieno[3,4-*c*]thiophene skeleton. This strategy was extended to the generation of selenium and tellurium analogs of **6**.

Reaction of 2,5-dimethoxycarbonyl-3,4-dicyanomethylthiophene **260**, which is readily available from the corresponding dibromide **259** by reaction with buffered potassium or sodium cyanide, with thionyl chloride and selenium oxychloride, gave thieno[3,4-*c*]thiophene **255** and selenolo[3,4-*c*]thiophene **258**, respectively (Scheme 50) [79]. This is the first example of the reaction of thionyl chloride with a carbanion acting as an S-transfer agent.

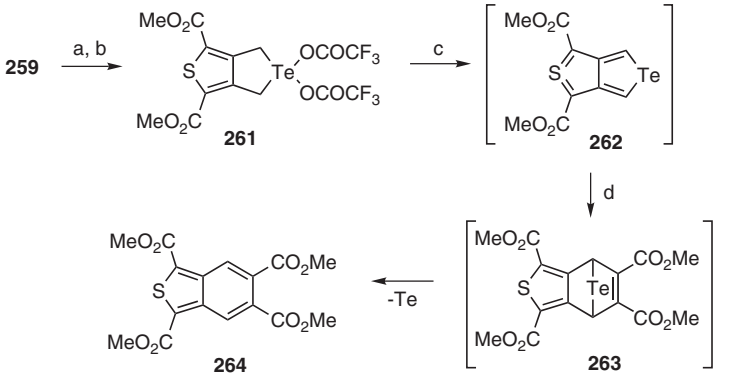


Compound	R^1	R^2	R^3	R^4
6	H	H	H	H
245	H	H	Me	Me
246	H	H	CO_2Me	CO_2Me
247	H	H	Bu^t	Bu^t
248	Me	Me	Bu^t	Bu^t
249	Ph	Ph	Ph	Ph
250	SR	SR	SR	SR
251	2-Thienyl	2-Thienyl	2-Thienyl	2-Thienyl
252	Br	Br	CN	CN
253	Br	Br	CO_2Me	CO_2Me
254	Br	Br	Br	Br
255	CO_2Me	CO_2Me	CN	CN
256	SBu^t	Ph	SBu^t	Ph
257	SBu^t	2-Thienyl	SBu^t	2-Thienyl

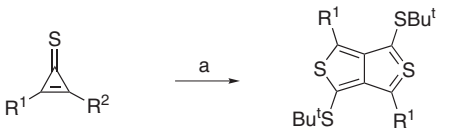
Fig. 14 Thieno[3,4-*c*]thiophenes [66–80]



Scheme 50 **a** NaCN, buffer (pH 9–10), 84%; **b** NEt_3, $SOCl_2$, or $SeOCl_2$, DCM, 84% (**255**), 10% (**258**) [79]



Scheme 51 **a** Te, DME, NaI; **b** CF_3CO_2Ag; **c** NEt_3, benzene, 5–6 h; **d** DMAD, 110–115 °C [81]



265a: R^1= Ph, R^2= SBu^t **256**: R^1= Ph
265b: R^1= 2-Thienyl, R^2= SBu^t **257**: R^1= 2-Thienyl

Scheme 52 **a** PPh_3, benzene, 50 °C, 20 h, 46% (**256**), 21% (**257**) [80]

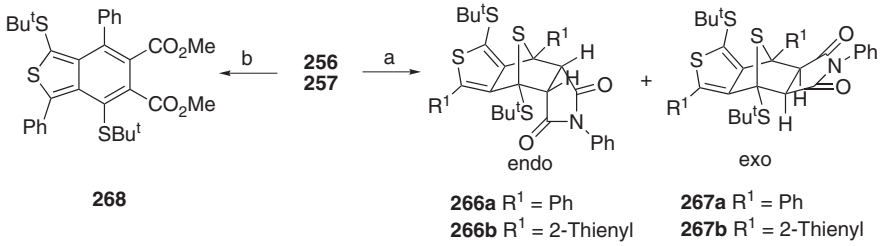
This strategy involving a Pummerer dehydration of sulfoxide and/or selenoxide is not applicable for preparation of tellurium analogs. The first diheteropentalene bearing the tellurolo[3,4-*c*]thiophene framework, e.g. **262**, has been generated from **259** using tellurium metal in the presence of sodium iodide in DME. Compound **262** appears to be stable in dilute solution for no more than 1–2 h and adds to DMAD across the 4,6-positions in the tellurophene part. The intermediate **263** loses tellurium and collapses to a 1,3,5,6-tetramethoxycarbonylbenzo[*c*]thiophene derivate **264** (Scheme 51) [81].

1,4-Bis(*tert*-butylsulfanyl)-3,6-diphenyl- **256** and 3,6-di(2-thienyl)thieno[3,4-*c*]thiophenes **257** were synthesized from 2-(*tert*-butylsulfanyl)-3-phenyl- and 3-(2-thienyl)cyclopropenethiones **265a,b** and triphenylphosphine in dry benzene at 50 °C (Scheme 52) [80].

5.2 Reactions of 2,5-Diheteropentalene Systems

Cycloaddition reactions of 2,5-diheteropentalene systems were studied. The 1,4-bis(*tert*-butylsulfanylphenyl **256** and 1,4-bis(*tert*-butylsulfanyl)-3,6-di-2-thienylthieno[3,4-*c*]thienophenes **257** were reacted with NPMI or DMAD in refluxing benzene (Scheme 53) [80]. The reaction of **256** with NMPI for 3 days gave the *endo*- and *exo*-cycloadducts (**266a** and **267a**) in 46% and 35% yields, respectively, while that with **257** gave the *endo*- and *exo*-cycloadducts (**266b** and **267b**) in 69% and 13% yields, respectively. Thus, the reactions of **256** and **257** with NPMI gave predominantly the *endo*-cycloadducts. The *endo*-selectivity was higher in the reaction with **254**, being different from that in the reaction with 1,3,4,6-tetrakis(alkylsu lfanyl)thieno[3,4-*c*]thiophenes, which gave selectively the *exo*-cycloadducts [74]. These results indicate that the *endo*/*exo* selectivity is governed by the steric effect of the substituents in the 4- and 6-positions on the cycloaddition in the 1- and 3-positions. The reaction of **256** with DMAD for 4 days gave 1,4-bis(*tert*-butylsulfanyl)-5,6-bis(methoxycarbonyl)-3,7-diphenylbenzo[*c*]thiophene **268** in 29% yield by loss of a sulfur atom from the cycloadduct.

The protonation of **256** and **257** with TFA gave 4-(*tert*-butylsulfanyl)-3,6-diphenyl-**269** and 4-(*tert*-butylsulfanyl)-3,6-di(2-thienyl)thieno[3,4-*c*]thiophene-1(3*H*)-thione **270** (Scheme 54). The treatment of **269** with sodium hydride and then isopropyl iodide

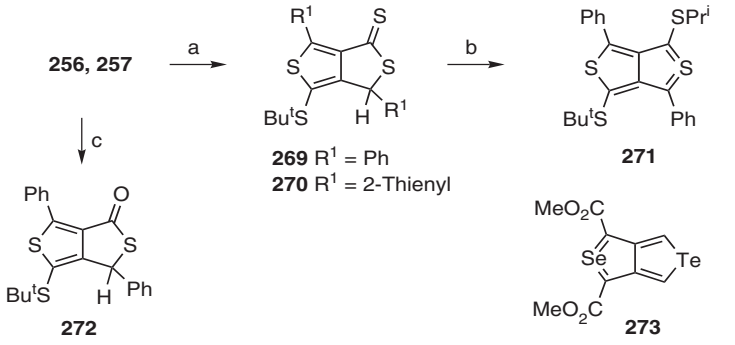


268

266a R^1 = Ph
266b R^1 = 2-Thienyl

267a R^1 = Ph
267b R^1 = 2-Thienyl

Scheme 53 **a** NPMI, benzene, reflux, 3 days, 46% (**266a**) and 35% (**267a**), 69% (**266a**) and 13% (**267b**); **b** DMAD, benzene, reflux, 4 days, 29% [74]



269 R^1 = Ph
270 R^1 = 2-Thienyl

271

272

273

Scheme 54 **a** TFA, benzene, RT, 20 h, 97% (**269**), 98% (**270**); **b** NaH, DMF, RT, 30 min; then Pr^iI, 30 min, 70%; **c** TFA, benzene–H_2O, RT, 20 h, 88% [80]

led to 4-(*tert*-butylsulfanyl)-3,6-diphenyl-1-(isopropylsulfanyl)thieno[3,4-*c*]thiophene **271** by the regeneration of the thieno[3,4-*c*]thiophene ring system, thus allowing the synthesis of other alkylsulfanyl-substituted thieno[3,4-*c*]thiophene derivatives. When the reaction of **256** with TFA was carried out in the presence of water, 4-(*tert*-butylsulfanyl)-3,6-diphenylthieno[3,4-*c*]thiophene-1(3*H*)-one **272** was produced [80].

The unstable 1,3-bis(methoxycarbonyl)selenolo- **273** [82] and 1,3-bis(methoxy carbonyl)tellurolo[3,4-*c*]thiophene **262** underwent Diels–Alder reactions with DMAD to produce cycloadducts, which lost selenium or tellurium and collapsed to tertramethoxycarbonylbenzo[*c*]thiophene **264** in low yields (Scheme 51) [81].

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New Trends in Chemistry and Application of Aromatic and Related Selenaheterocycles

J. Młochowski and M. Giurg

Abstract Progress in the chemistry of compounds having π-conjugated selenaheterocyclic systems is presented. The review concentrates on the most representative selenaheterocycles: selenophene, selenazoles, selenadiazoles, as well as on seleninium salts. Their aromaticity is discussed and the chemical properties are illustrated by the most characteristic reactions. Various approaches to the synthesis of different selenaaromatic ring systems are presented. A number of selenaaromatic compounds and their nonconjugated analogs are indicated as reagents and catalysts for organic synthesis, as biological response modifiers of practical importance as pharmaceuticals, and as new materials for electronics.

Keywords Heterocyclic compounds, Selenadiazoles, Selenazoles, Seleninium salts, Selenophene

Contents

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Abbreviations

AIBN	α,α′-Azaisobutyronitrile
ASE	Aromatic stabilization energy
BETS	Bis(ethylenedithio)tetraselenafulvalene
COD	Cyclooctadiene
DMAD	Dimethyl acetylenedicarboxylate
DRE	Dewar resonance energy
GPx	Glutathione peroxidase
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoric triamide
HOMA	Harmonic oscillator model of aromaticity
IL	Interleukine
IFN	Interferon
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
MCPBA	*m*-Chloroperoxybenzoic acid
MIC	Minimal inhibitory concentration
NICS	Nucleus independent chemical shifts
OLED	Organic light-emitting diode
OTFT	Organic thin film transistor
PBL	Peripheral blood leukocytes
PDSE	Poly-1,2-bis(seleninyl)ethene
PEDOS	Poly-3,4-ethylenedioxyselenophene
PEDOT	Poly-3,4-ethylenedioxythiophene
PS	Polyselenophene
RF-ID	Radio frequency identification
TBHP	*t*-Butyl hydroperoxide
TMEDA	1,1,4,4-Tetramethylethylenediamine
TMSF	Tetramethylselenafu-lvalene
TNF	Tumor necrosis factor

1 Introduction

Interest in the chemistry and use of different selenium-containing heterocyclic compounds, including those having aromatic systems, as potential pharmaceuticals, as new materials, and as reagents and catalysts has expanded rapidly during last three decades and a lot of works in this field have been published.

This review covers the scientific literature from 1995 to the present, but includes several significant earlier references where necessary for discussion. A number of reviews on selenaheterocyclic compounds, or more generally on organoselenium compounds including selenaheterocycles, have been published during last decade [1–16]. In most of them, selenium-containing heteroaromatic ring have been mentioned. There are also reports and some reviews dealing with selenaaromatic compounds and their nonaromatic analogs of practical importance as reagents and catalysts [10, 17, 18], as pharmaceuticals [10, 19–21], and as materials for electronics [22–25]. Since referring of all original papers recently published would be beyond of the scope of this review we refer to those that, in our opinion, emphasize modern trends in the chemistry and use of selenaaromatic compounds and their prospective nonaromatic analogs.

Several of these works have been carried out in our laboratory, and we present them in this article, referring briefly to some new unpublished results. We would like to apologize to anyone who finds our description of her or his work inadequate or whose work we have omitted.

2 Aromatic Selenaheterocyclic Systems

The best known selenaaromatic compounds have a five-membered ring containing only selenium or selenium and adjacent or nonadjacent nitrogen atoms. Selenophene (**1**), selenazoles (**2**, **3**), selenadiazoles (**4**, **5**) are presented in Fig. 1, together with their analogs with an annulated benzene ring. Bicyclic heteroaromatic selenium-containing systems with ring junction sulfur or selenium atom, such as for example **6** and **7**, are less common compounds and have been covered only in the older literature. As well as five-membered rings containing neutral selenium atom, the cationic forms, e.g., **8** and **9** (Fig. 2) are also possible. These cations exist in the stable selenonylium salts.

Selenaaromatic six-membered ring systems are known only in the ionic seleninium forms (**10**), like the pyrylium cation.

The structures of selenaaromatic compounds are closely related to those of analogous sulfur compounds. The best known is selenophene (**1**). As for thiophene, the idea can be offered in terms of resonance theory (Fig. 3). This means that outer valence shell resonance structures **1a–d** may be hybridized into an aromatic sextet. In these cases, selenium acts as an electron acceptor and negative charge is localized on the selenium atom. In contrast, structures **1e–h** have octet formulation not involving valence shell expansion. Selenium acts as electron donor and in these cases positive charge is localized on the selenium atom (Fig. 3).

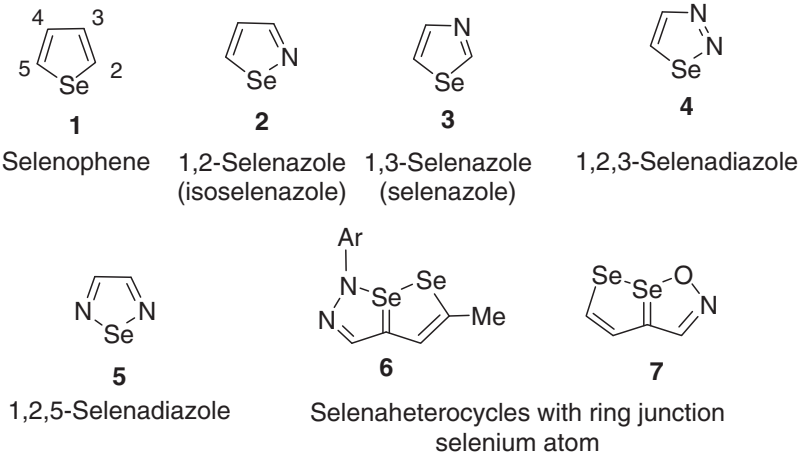


Fig. 1 Five-membered neutral selenaaromatic ring systems

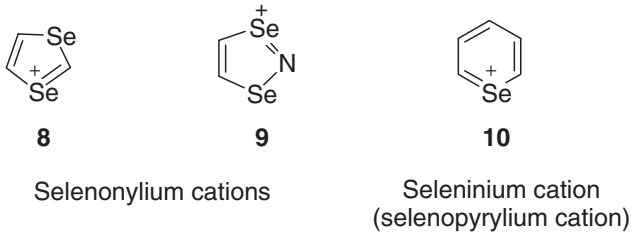


Fig. 2 Ionic selenaaromatic ring systems

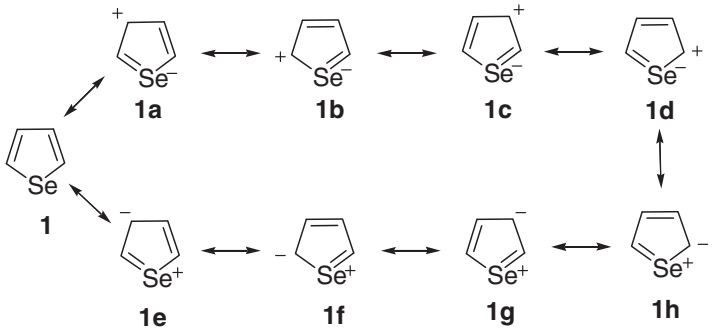


Fig. 3 Resonance structures of selenophene

The fact remains that selenophene and its derivatives have aromatic character. This statement is, however, not easy to substantiate with quantitative data mainly because there are too many ambiguities for parent five-membered ring heterocycles. Some aromaticity indices for five-membered rings with one heteroatom, among them selenophene, were summarized and estimated values for thiophene and selenophene were similar [26]. The data obtained from photoelectron ionization energies show that the aromatic stabilization in thiophene is slightly larger than for selenophene [27].

The decreasing order of aromaticity based on DRE values (in kcal mol^{-1}) is: benzene (22.6) > thiophene (6.5) > selenophene > pyrrole (5.3) > tellurophene > furan (4.3). In benzoderivatives the effect of the heteroatom is similar to the azole series and the decreasing scale of aromaticity is benzo-2,1,3-selenadiazole > benzo-2,1,3-thiadiazole > benzo-2,1,3-oxadiazole [28].

Another theoretical criterion applied to estimation of aromaticity of homo- and heteroaromatic ring system is aromatic stabilization energy (ASE). Based on this approach, the aromatic sequence of five-membered ring systems (ASE in kcal mol^{-1}) is: pyrrole (20.6) > thiophene (18.6) > selenophene (16.7) > phosphole (3.2) [29].

According to geometric criterion HOMA, based on the harmonic oscillator model [30–33], thiophene is more aromatic than pyrrole and the decreasing order of aromaticity is thiophene (0.891) > pyrrole (0.879) > selenophene (0.877) > furan (0.298) > phosphole (0.236) [29].

For selenophene (**1**), selenazoles (**2**, **3**) as well for selenadiazoles (**4**, **5**) the ^{1}H NMR data of ring hydrogens are consistent with their aromaticity. The chemical shifts of ring protons signals can range from 6.8 ppm with an electron-donating substituent to above 10.00 ppm with an adjacent electron-withdrawing group. They also vary depending on the influence of the heteroatom. Ring proton chemical shifts (δ, ppm) of four representative five-membered selenaaromatic compounds are give in Fig. 4 [2, 3, 6, 26].

The chemical shifts of all ring protons of 1,3-chalcogenoselenonylium cations fall in the broad range 9.40–13.40 ppm and are quite sensitive to the adjoining heteroatoms [34]. It is in agreement with diamagnetic ring current characteristics for strongly electron-deficient 6π heteroaromatic rings.

Among the aromatic indexes, a magnetic criterion, nucleus-independent chemical shifts (NICS) has become the most widely used aromaticity probe due to its simplicity and efficiency [35, 36]. NICS is defined as a negative value (in ppm) of the absolute shielding computed at a ring center (or some other interesting point of the system). Rings with negative NICS values qualify as aromatic, and the more negative the NICS, the more aromatic the rings. For five-membered heteroaromatic

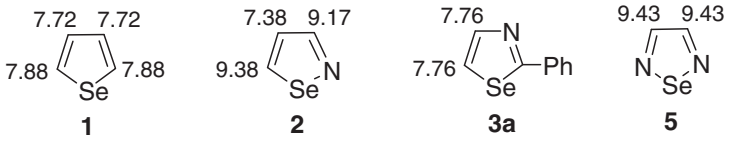


Fig. 4 Ring proton ^{1}H NMR chemical shifts (ppm) of four selenaaromatic compounds measured in $CDCl_3$ (**1**, **2**, **3a**) or in $(CD_3)_2SO$ (**5**)

compounds, the aromaticity decreases: pyrrole (−14.9) < thiophene (−13.8) < selenophene (−12.8) < furan (−12.3) < phosphole (−5.4) and order is similar to that estimated from ASEs [29]. Because NICS is a local rather than a global aromatic index, it characterizes individual rings in a polycycle, rather than the aromaticity of the entire molecule. NICS values for 1-benzoselenophene are −8.74 (benzene ring) and −9.29 (heterocyclic ring), while for 2-benzoselenophene they are −4.12 and −13.94, respectively, and are similar to these estimated for 1-benzothiophene (−9.10, −10.35) and 2-benzothiophene (−5.06, −14.86) [29].

In a spectral UV–VIS study of a series of chalcogenopyrylium dyes it has been shown that the aromaticity of the heterocycles decreases with the size of the chalcogen, whereas the bathochromic effect increases from the oxygen to tellurium [7]. The aromaticity index based on data from experimentally determined bond lengths, which yield statistically evaluated bond orders, has been proposed and applied to neutral and ionic five-membered selenaheterocycles. A reasonable parallel also exists between the aromaticity index and resonance energies [37].

The aromaticity of selenaphospholes and selenadiphospholes has been discussed on the basis of photoelectron spectroscopic and quantum chemical investigations and by X-ray structural characterization of the η′-Cr $(CO)_5$ complexes [27, 38–40].

X-ray structure determination of diselenazolylium salts, tetrachloronickelate (**11**) and perchlorate (**12**), shows that the hetero-rings both of these cations are planar delocalized 6π-electron systems (Fig. 5) [41, 42].

A recent study of proton transfer from rhenium Fisher-type carbine complexes (**13**) shows that the reactions lead to the formation of an aromatic product (**14**), following the same rules as reactions that lead to the formation of products stabilized by simple resonance. The conjugate bases of these carbine complexes represent aromatic heterocycles, i.e., substituted furan, selenophene, and thiophene derivatives, respectively. The aromatic stabilization of these heterocycles is known to follow the order furan < selenophene < thiophene (Scheme 1) [43].

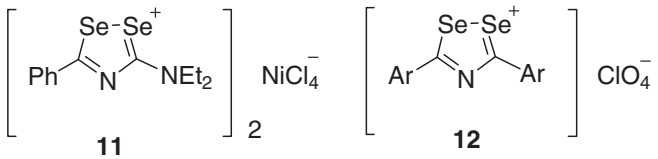
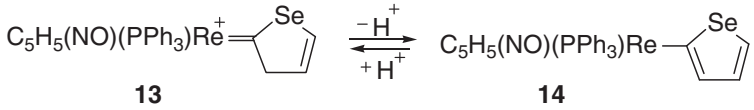


Fig. 5 Aromatic diselenazolylium salts



Scheme 1 Proton transfer from carbine complex **13** to give aromatic product **14** AU1

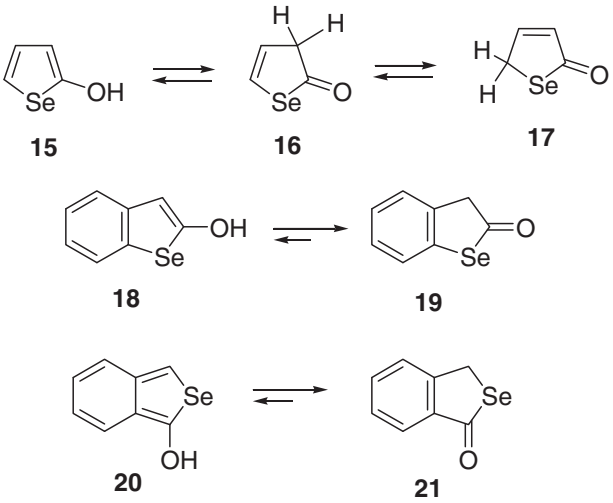
3 Chemical Properties of Selenaheterocyclic Rings

3.1 Tautomerism

Tautomeric equilibria are very important intramolecular proton-transfer reactions, which by definition are associated with changes in π-electron distribution. In general, π-electron delocalization plays a principal role in tautomeric systems and affects tautomeric preferences. However, other internal effects (such as stability of functionalities, *n*–π or Y-conjugation, push-pull effect, aromaticity, substituent effects, or intramolecular H-bonding) and external influences (e.g., solvent, ionization, temperature) may change this general behavior. Analysis of the relationship between characteristics of π-electron delocalization and aromaticity of heterocyclic systems and tautomeric equilibria have been reviewed elsewhere [28, 44–46].

Despite broad theoretical and experimental studies on tautomerism of oxygen-, nitrogen-, and sulfur-containing heteroaromatic compounds only little attention has been paid to selenaheterocycles. Although presence of a hydroxy-, thio-, or amino-substituent in selenium-containing five- and six-membered heterocycles could lead to various tautomeric forms, only prototropic keto–enol tautomerism in selenophene derivatives was investigated [26, 47, 48].

The parent 2-hydroxyselenophene possesses in principle three tautomeric forms (**15**, **16**, **17**) but the oxo form (**17**) predominates. In the 2-hydroxy-1-benzoselenophene (**18**) and 1-hydroxy-2-benzoselenophene (**20**), where loss of heterocyclic ring resonance energy on tautomerism to **19** and **21** will be much less than for the non-annelated heterocycle, the latter oxo tautomers are preferred (Scheme 2) [26].



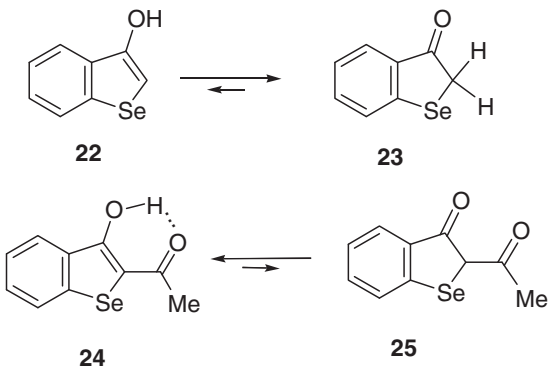
Scheme 2 Oxo-tautomers **17**, **19**, and **21** are preferred

3-Hydroxy-1-benzoselenophene (**22**) and its 2,2-disubstituted derivatives exist preferentially as the oxo tautomer (**23**) (Scheme 3). A similar effect was observed for 3-hydroxyselenophene. Introduction of the acetyl group at the 2-position promotes enolization and for 2-acetyl-3-hydroxy-1-benzoselenophene the enol (**24**) not oxy form (**25**) is preferred, presumably by virtue of the extra stability by intramolecular hydrogen bonding. The broad IR absorption band $\upsilon_{OH\cdots O}$ = 3005–1930 cm^{-1} and the band of the exocyclic carbonyl group $\upsilon_{C=O}$ = 1583 cm^{-1} both shifted to lower frequencies, as well as the signal for the acid proton (δ = 12.86 ppm) in the ^{1}H NMR spectrum provide evidence for structure **24**. The same effects were observed for other 2-acyl-3-hydroxy-1-benzoselenophenes [47, 48].

For 2,5-dihydroxyselenophene, the 2,5-dioxo structure is well established and there is no evidence for intervention of any enolic species.The 2- and 3-sulfanyl derivatives of selenophene exist in the sulfanyl form [26]. No detailed study has been made of the generally unstable amino derivatives which, from the very limited information available, appear to exist as such.

A dipole moment study of selenopyran-4-ones, selenon-4-ones, and selenoxanthones were used as the basis of an approach to the aromacity of these heterocycles. The contribution to a polar form decreases in the order O > S > Se > Te [7].

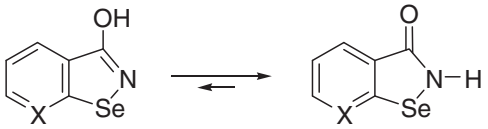
The isoselenazole ring in unsubstituted 3-hydroxy-1-benzo-1,2-selenazole (**26**) and in its 7-azaanalog (**27**) exists in nonaromatic amide form such as in **28** or **29** (Scheme 4). The amide proton is easily exchanged, via potassium salt, by alkyl, acyl, or sulfonyl groups. The additional evidence for amide structure is based on spectral data. For example, the amide band $\upsilon_{C=O}$ = 1646 cm^{-1} in the IR spectrum and the broad singlet at 9.34 ppm in the ^{1}H NMR spectrum were observed for **29** [49–51].



22 **23**

24 **25**

Scheme 3 Oxo-tautomer **23** is preferred, but introduction of an acetyl group promotes enolization so that the enol form **24** is preferred



26 X = CH
27 X = N

28 X = CH
29 X = N

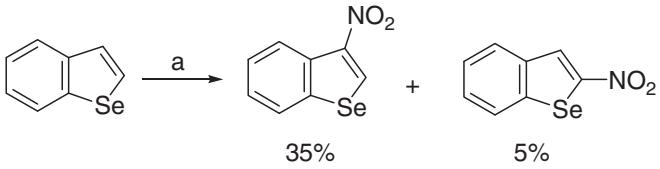
Scheme 4 The isoselenazole ring exists in nonaromatic amide form (**28**, **29**)

3.2 Reactions on Carbon Atom

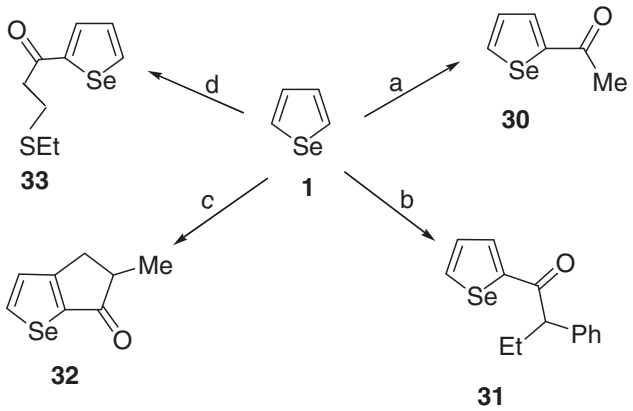
Many of the existing reactions of selenaheterocycles were covered in the older literature [1–9, 14, 26, 34]. It has been long known that selenophene and selenazoles undergo the same electrophilic substitution reactions as their sulfur analogs, but reacting somewhat faster. Depending upon the reaction, selenophene reacts 2–50 times faster than thiophene [15]. Selenophene is reported to be unstable to acid because of protonation at the 2-position. The formed cation undergoes subsequent reactions. Selenophene, selenazoles, and selenadiazoles undergo preferential α- rather than β-electrophilic substitution. This is rationalized in terms of the more effective delocalization of charge in the intermediate σ-complex leading to α-substitution than in the intermediate leading to β-substitution. In general, the α-directing effect of the heteroatom is furan >> thiophene ≈ selenophene >> pyrrole. 1-Benzoselenophene is generally more reactive toward electrophilic reagents, although, like 1-benzothiophene, it undergoes mainly β-substitution (Scheme 5).

The presence of one azine-like ring nitrogen atom (selenazoles) or two nitrogen atoms (selenadiazoles) decreases reactivity to electrophilic reagents. Strongly π-electron deficient systems as selenonylium, seleninium, and selenazinium salts are resistant to electrophilic substitution. Although a variety of substitution reactions at selenophene carbon atoms (such as sulfonation, halogenation, formylation, acylation, chloromethylation, trifluoromethylsulfonylation, diazo-coupling and palladium(II)-catalyzed oligomerization) have been known for many years several of them have been recently revised and improved. 2-Bromoselenophene is conveniently prepared by bromination of selenophene with NBS [52], and 2-iodoselenophene is obtained by treatment of selenophene with *n*-BuLi followed by reaction with iodine [53]. Reaction of the parent heterocycle with iodine in the presence of mercury(II) acetate affords 2,3,4,5-tetraiodoselenophene in almost quantitative yield [54]. Formylation of selenophene under Vilsmeier–Haack conditions yields 2-formylselenophene, while 2-acetylselenophene (**30**) was prepared by acylation with acetic anhydride in the presence of tin chloride, perchloric acid, or phosphoric acid [55, 56]. Other 2-acylselenophenes (**31–33**) were prepared by the reactions presented in Scheme 6 [57–59].

Electrophiles react with 2-substituted 1,3-selenazoles at the 5-position. Nitration of 2-alkyl-1,3-selenazoles and 2-acetylamino-1,2-selenazole affords 5-nitroderiva-



Scheme 5 **a** Fuming HNO_3, $(AcO)_2O$, 0 °C



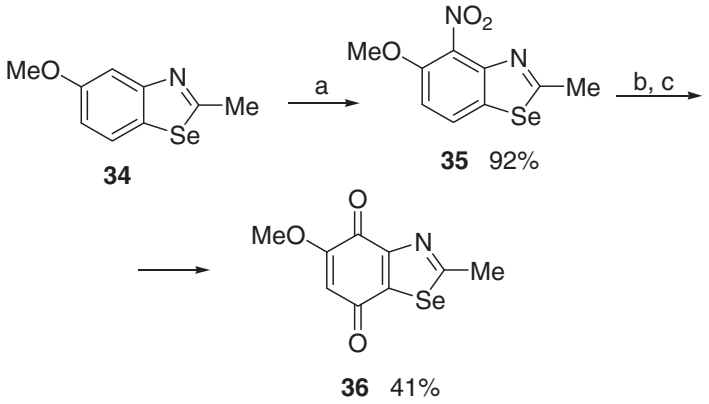
Scheme 6 **a** Ac_2O, H_3PO_4, 80–90 °C; **b** $PhCH(C_2H_5)COOH$, $(CF_3CO)_2O$; **c** $CH_2=C(CH_3)COOH$, PPA, CH_2ClCH_2Cl, 80 °C; **d** $EtS(CH_2)_2COF$, BF_3, CH_2Cl_2

tives under relatively mild conditions [3]. 2,4-Disubstituted 1,3-selenazoles were coupled with diazonium tetrafluoroborate, at 5-position to azo compounds [60]. 1-Benzo-1,3-selenazoles react with electrophiles in the benzene ring. An example is nitration of 2-methy-5-methoxy-1-benzo-1,3-selenazole (**34**) to the nitroderivative (**35**), subsequently converted to 1,4-quinone (**36**) (Scheme 7) [61].

Bromination and nitration of substituted 1,2-selenazoles occurs at the 4-position but products undergo decomposition. 3-Methyl-5-phenyl-1,2-selenazole reacts with a mixture of concentrated nitric and sulfuric acids to give 3-methyl-4-nitro-5-(4-nitrophenyl)-1,2-selenazole in 54% yield, accompanied by other nitroderivatives. Bromination and nitration of 1-benzo-1,2-selenazoles results in substitution in the benzene ring and does not occur at the 3-position; thus nitration afforded an almost equimolar mixture of 5-nitro- and 7-nitro-1-benzo-1,2-selenazoles in an overall quantitative yield, while bromination led to a mixture of mono-, di-, and tribromo compounds [2, 10].

Selenophene does not react with nucleophilic reagents by substitution or addition but only by proton transfer. Other selenaheterocycles such as 1,2- and 1,3-selenazoles, selenadiazoles, and particularly seleninium salts are susceptible to nucleophilic attack at the carbon atoms of selenaaromatic rings.

Base-catalyzed hydrogen isotope exchange in inactivated selenophenes occurs only in highly basic media. The relative rates of exchange of deuterium at the α-position in furan, thiophene, and selenophene in 0.4 M *t*-BuOK/DMSO



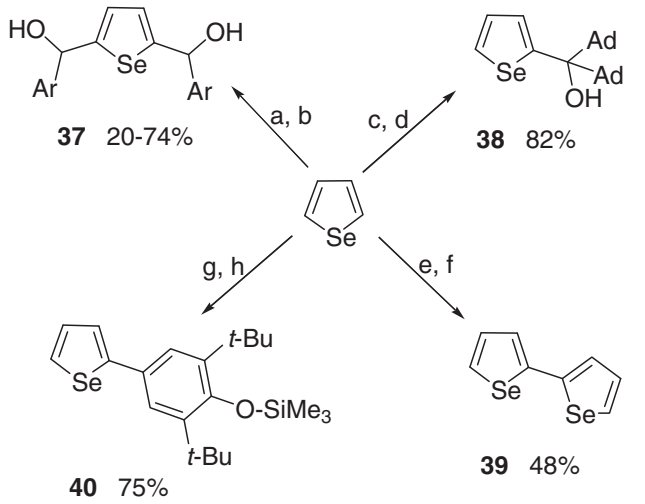
Scheme 7 **a** HNO_3, H_2SO_4, 20 °C; **b** $SnCl_2$, HCl, H_2O, 60 °C; **c** H_2O, KH_2PO_4, potassium nitrosodisulfonate, 20 °C

have been determined to be 1:500:700. This has been explained by the enhanced stabilization of the β-carboanions through *d*–s overlap in the latter two systems [55, 62].

Organolithium reagents attack selenophene, as strong bases, abstracting ring hydrogen atoms. Selenophene and 1-benzoselenophene undergo exclusive α-lithiation. Metallated selenophenes easily react with different electrophilic reagents to give α-mono- or α,α′-disubstituted products. Selenophene was formylated by treatment with *n*-butyllithium and then with *N*,*N*-dimethylformamide to give 2,5-diformylselenophene [63]. 2,5-Di(hydroxyarylmethyl)selenophenes (**37**) were obtained in similar reaction conditions with use of the benzaldehydes or pyridine carbaldehydes [64–68]. Other examples of the reactions of α-metallated selenophene are hydroxyalkylation with ketone to **38** [69], coupling to 2,2′-diselenienyl (**39**) [70, 71], introduction of sulfur-containing functional groups [72] and α-arylation to **40** with aryliodide [73] (Scheme 8).

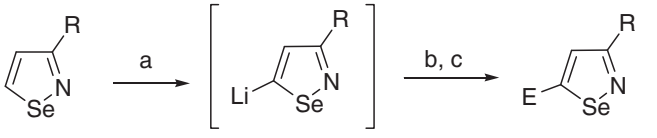
1,2-Selenazoles undergo ring opening upon treatment with nucleophilic (or reducing) agents. The nucleophiles mostly attack the electrophilic selenium and the Se–N bond is cleaved, but with LDA metallation of the 1,2-selenazoles (**41**) takes place at the 5-position. The resulting lithium derivative (**42**) can react with electrophiles to give the substitution product **43** (Scheme 9) [10].

1-Benzo-1,2-selenazoles react with nucleophiles by substitution at the 3-position or cleavage of the heterocyclic ring. 3-Amino-1-benzo-1,2-selenazole was obtained in 36% yield by amination with potassium amide in liquid ammonia. In 1,2-selenazolium salts, the vicinity of the positively charged nitrogen activates the 3-position toward nucleophiles. The conversion of 3-chloro-1-benzo-1,2-selenazolium salts (**44**) to 3-amino-1-benzo-1,2-selenazoles (**45**) is an example (Scheme 10). The reaction proceeds through initial addition of ammonia and ring opening, followed by recyclization [10, 74].



Ar = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 2-py, 3-py; Ad = adamantyl

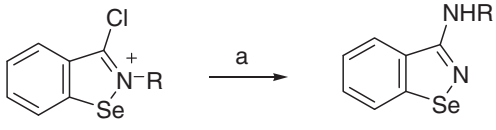
Scheme 8 **a** *n*-BuLi, *n*-hexane, TMEDA, 20 °C then reflux; **b** PhCHO, −10 °C then 20 °C; **c** *n*-BuLi, *n*-hexane, 20 °C; **d** AdCOAd, Et_2O, 20 °C; **e** *n*-BuLi, Et_2O, −78 °C; **f** $CuCl_2$, THF, −78 °C; **g** *n*-BuLi, Et_2O, −20 then 0 °C, $ZnCl_2$; **h** $Pd(PH_3)_4$(cat), 1-($OSiMe_3$)-2,6-di(*t*-Bu)-4-IC_6H_2, 20 °C



41 **42** **43**

E = D, Me, CHO, COOH

Scheme 9 **a** LDA, THF, −78 °C; **b** E^+; **c** H^+



44 **45**

Scheme 10 **a** Gas. NH_3, benzene, 20 °C R = alkyl, Ph

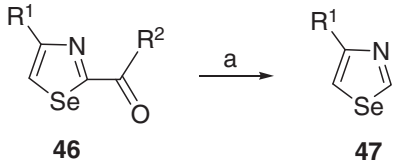
The metallation of neither 1,3-selenazoles nor 1-benzo-1,3-selenazoles has been reported. Nucleophilic reagents replace some substituents present at the 2-position. Displacement of the 2-thiol group of 2-thiol-1-benzo-1,3-selenazole to prepare 2-aminoderivative is an example [3]. The 2-chlorine atom is easily substituted by an amino group when treated with propargylamine [75].

Alkaline deacylation of 2-acyl-4-aryl-1,3-selenazoles (**46**) results in removal of the acyl group, and the parent compounds (**47**) are produced in good to fair yields (Scheme 11) [76]. The selenazolium salts are activated toward nucleophiles at the 2-position. The salts (**48**) react with DMSO-d_6 to give the 2-deuteroxy derivatives (**49**) (Scheme 12) [77].

Selenadiazoles do not undergo electrophilic substitution in the heterocyclic moiety, but in their benzo derivatives substitution occurs at positions 4 and 7 of the benzene ring. Nitration of benzo-2,1,3-selenadiazole (**50**) gave the 4-nitroderivative (**51**) [78, 79]. Halogenation affords the corresponding 4,7-dihaloderivatives, being useful intermediates for introduction of different groups by nucleophilic substitution [6, 66, 67]. Nucleophilic substitution in the benzene ring is promoted by the electron-deficient character of the hetero-ring. Substitution of bromine atoms in various 4-bromobenzo-2,1,3-selenadiazoles by nitrogen nucleophiles was extensively investigated and the conversion of **52** to **53** is an example (Scheme 13) [80, 81].

1,2,3-Selenadiazole and 4-substituted 1,2,3-selenadiazoles are deprotonated at the 5-position by strong bases to form carboanions, which collapse with loss of N_2 to give selenolate salts R–C≡C–Se^-K^+. The selenolates are versatile synthons whose usefulness has been outlined in the reviews [6, 82].

The chemistry of seleninium salts is dominated by the electrophilicity of the cationic nucleus. The strongly electron-deficient heterocyclic ring and the annulated benzene ring are deactivated toward electrophilic attack. The nucleophiles are added to α- or γ-carbons and the heterocyclic ring is dearomatized [7].



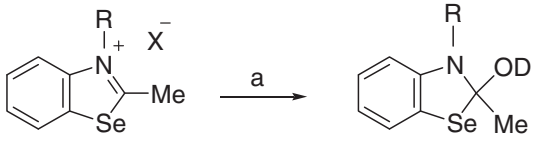
46 **47**

60-90%

R^1 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$

R^2 = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$

Scheme 11 **a** Aq. NaOH, EtOH, Δ

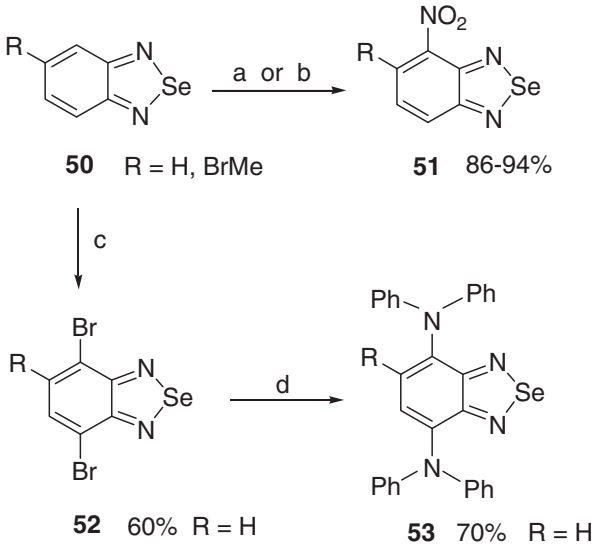


48 **49**

R = CH_2COOH, Et, *n*-C_5H_{11}, *n*-$C_{10}H_{21}$

X = Br, I

Scheme 12 **a** DMSO-d_6, 50 °C

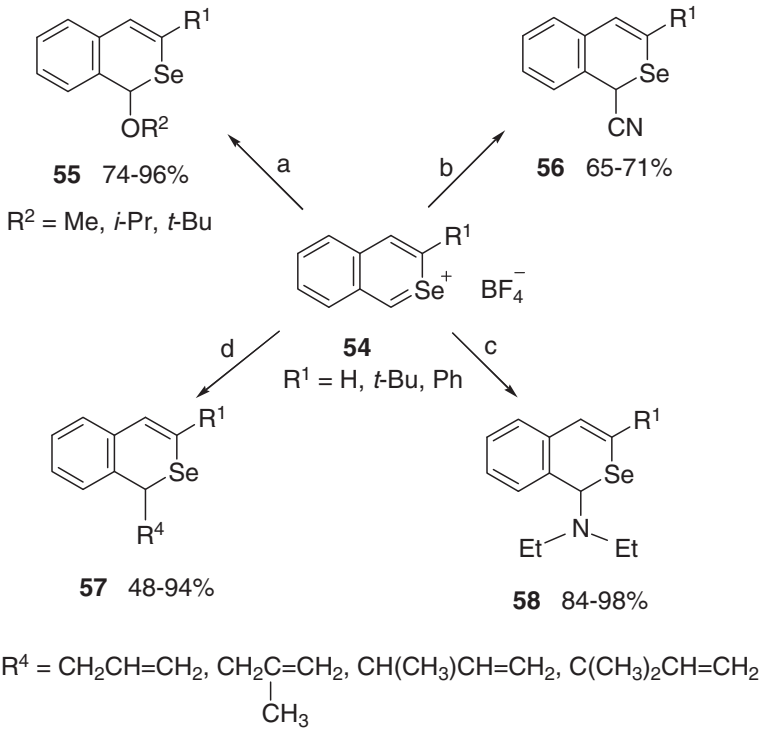


Scheme 13 **a** Eaton's reagent, HNO_3, H_2O, 20 °C; **b** 70% aq. HNO_3, H_2SO_4, 20 °C; **c** Br_2, Ag_2SO_4, H_2SO_4, 20 °C; **d** *t*-BuNa, P(*t*-Bu)$_3$, Pd(dba)$_2$, toluene, 80 °C

The reactions of selenopyrylium and 1- and 2-selenochromylium salts with nucleophilic reagents were applied in the synthesis of selenopyranes, 1-selenochromenes, and 2-selenochromenes. 2,4,6-Triphenylselenopyrylium tetrafluoroborate reacts with phenylmagnesium bromide to give 2,4,4,6-tetraphenyl-4*H*-selenopyran-4-one [83]. 4-Methyl-2,4-dibutylselenopyrylium hexafluorophosphate is oxidized with air in basic conditions to 2,6-di-*t*-butylselenopyran-4-one [84]. 1-Selenochromylium tetrafluoroborate treated with nucleophilic reagents such as alkoxides, primary or secondary amines, lithium aluminum hydride, Grignard reagents, or azides gives 4-substituted-2*H*-1-selenochromenes and 2-substituted-4*H*-1-selenochromenes. The addition of nucleophile to 2-benzoselenopyrylium cation is more selective and the substituent is introduced in the 1-position. 1-Unsubstituted 2-selenochromenes were converted into 2-benzoselenopyrylium salts (**54**) by treatment with Ph_3C^+ BF_4^-, and the reaction of **54** with nucleophilic reagents (alcohols, cyanide, acetone, primary and secondary amines, Grignard reagents, and others) afforded the corresponding 1-substituted 2-selenochromenes, e.g., **55**–**58** (Scheme 14) in high yields [85–89].

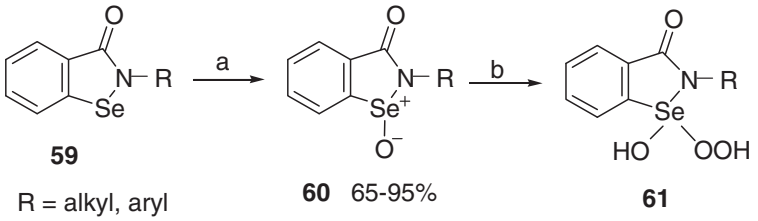
3.3 Reactions on Heteroatom

The principal electrophiles to attack ring selenium are either oxidants or alkylating agents. Oxidation of substituted selenophenes and 2-benzoselenophene with an excess of 2,2-dimethyldioxirane leads to 1,1-dioxides, whereas oxidation of



Scheme 14 **a** R^2ONa or R^2OK, benzene or PrOH, 20 °C; **b** NaCN, MeCN, 18-crown-6, 20 °C; **c** Et_2NH, benzene, 20 °C; **d** R^4SnBu_3, CH_2Cl_2, 20 °C

1-benzoselenophene with MCPBA result in its 1-oxide. Selenophene 1-oxide spontaneously decomposes and even its ring-substituted derivatives are unstable compounds [90, 91]. Dibenzoselenophene forms the 5-oxide when treated with peracetic acid, a compound also obtained when the 5,5-dibromide is reacted with diluted aqueous sodium hydroxide [58]. Oxidation of selenium in the nonaromatic heterocyclic moiety in benzisoselenazol-3(2*H*)-ones (**59**) with hydroperoxides or peracids gives 1-oxides (**60**) (Scheme 15) [10, 18, 92]. When oxidant (H_2O_2 or TBHP) is used in a large excess the unstable hydroperoxyselenuranes (**61**) are formed. They are postulated active intermediates involved in the hydroperoxide oxidation of various organic compounds catalyzed by **60** [10, 16–18, 93]. Optically active benzisoselenazol-3(2*H*)-one 1-oxides with stereogenic center at the selenium atom were also obtained [10, 16, 94–96]. The selenium atom in benzisoselenazol-3(2*H*)-ones, isoselenazolidines, and their open-chain analogs interact with active oxygen species present in the living cells and deactivate them in a glutathione peroxidase (GP_x) way [20, 21].



Scheme 15 **a** 30% aq. H_2O_2, MeCN, 20 °C; **b** 30% aq. H_2O_2 (excess), MeCN, 20 °C

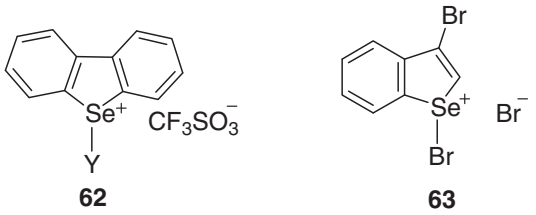
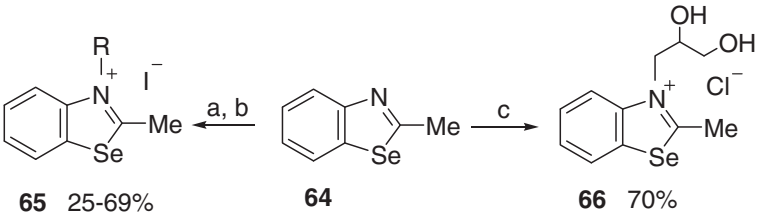


Fig. 6 Selenienylium salts

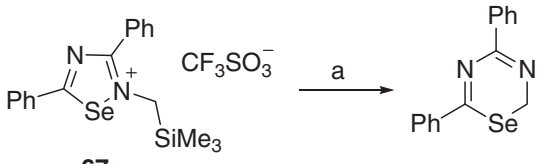


Scheme 16 **a** $HClO_4$; **b** RI, MeCN, Δ; **c** HO–CH_2–CH(OH)–CH_2Cl

When **59** or **60** are treated with a reducing agent such as hydrazine or triphenylphosphine, the Se–N bond is cleaved to give 2-(carbamoyl)phenyl diselenides [92]. The ring cleavage with thiols leads to the selenosulfides [10, 97].

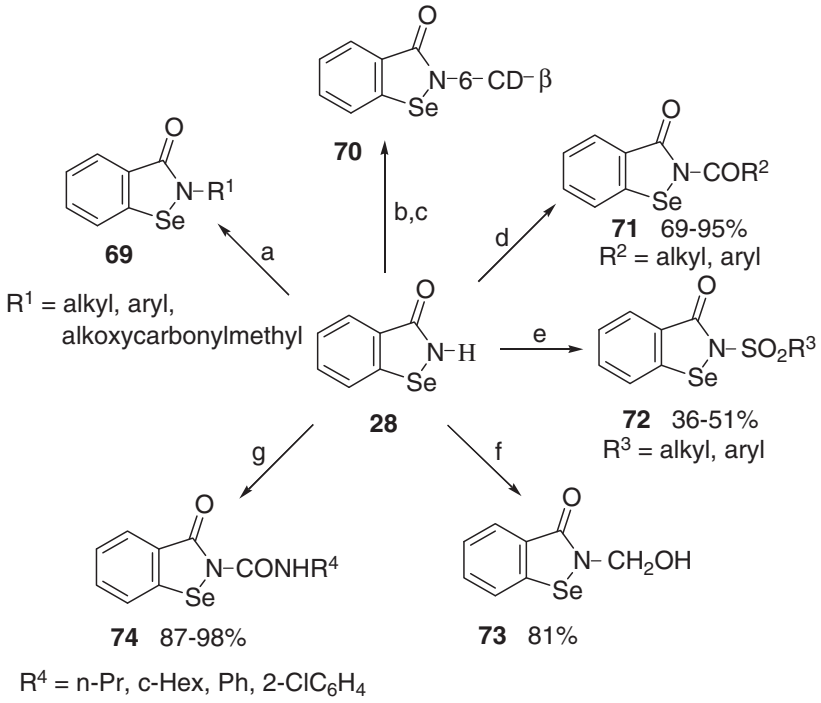
Dibenzoselenophene is readily alkylated to the selenienyl salts (**62**), which are powerful methylation and trifluoromethylation agents [98, 99]. Halogens preferentially attack α-carbon in selenophenes but the 1,2-dibromo-1-benzoselenophenium bromide (**63**) was found among the bromination products of 1-benzoselenophene (Fig. 6) [100].

In the aromatic selenazaheterocyclic systems, the nitrogen atom is a nucleophilic center readily quaternized by alkylating or acylating agents. An illustrative example is *N*-alkylation of 2-methyl-1-benzoselenazole (**64**) to the 2-methyl-1-benzoselenazolium salts (**65** and **66**) (Scheme 16) [101, 102].



67 **68** 79%

Scheme 17 **a** CsF, CH_2Cl_2, 20 °C



Scheme 18 **a** RX, KOH, 20 °C (X = halogen); **b** KOH, DMF, H_2O, −15 °C; **c** β-CD-6-I, 60 °C; **d** R^3COCl, NaOH, K_2CO_3, Bu_4N^+ I–, benzene, 20 °C or 50 °C; **e** R^3SO_2Cl, NaOH, Et_2O, 20 °C; **f** HCHO, H_2O, reflux; **g** R^4NCO (excess) or toluene, reflux

The quaternary salts of selenium-nitrogen heterocycles are labile to nucleophiles and can be converted to other heterocyclic systems by ring expansion [82, 103]. An example is conversion of 1,2,4-selenadiazolium trifluoromethane sulfonate (**67**) into 1,3,5-selenadiazine (**68**) (Scheme 17) [104]. 2,3-Dimethyl-1-benzo-1, 3-selenazolium tetrafluoroborate is readily condensed with aromatic aldehydes to 2-styrylselenazole [105] or treated with sodium hydride to give 3-methyl-2-methylene-2,3-dihydro-1-benzo-1,3-selenazole [106].

Because of growing interest in benzisoselenazol-3(2*H*)-ones as bioactive species and oxygen-transfer agents, several papers have dealt with an electrophilic attack at

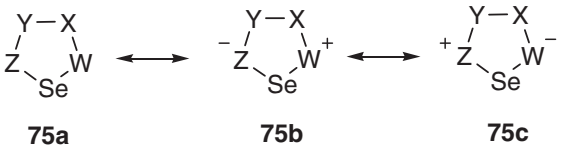


Fig. 7 Nonpolar and polar resonance structures of five-membered selenaaromatic rings

the amide nitrogen of unsubstituted benzisoselenazol-3(2*H*)-one (**28**). Alkylation using KOH and alkyl, allyl halide or halocarboxylic ester gave 2-substituted derivatives (**69**) [107, 108]. The cyclodextrin derivatives (**70**) were designed as an artificial enzyme, and prepared by reaction of **28** potassium salt with 6-iodo-β-cyclodextrin (β-CD-G-I) [109]. The *N*-acylation and *N*-sulfonylation of **28** with carboxylic acid chlorides or sulfonyl chlorides is an efficient method for the synthesis of 2-acyl and 2-sulfonylbenzisoselenazol-3(2*H*)-ones (**71**, **72**) [50]. A reaction with formalin resulted in *N*-(hydroxymethyl)benzisoselenazol-3(2*H*)-one (**73**), while reaction with isocyanates yielded the 2-carbamoylbenzisoselenazol-3(2*H*)-ones (**74**) (Scheme 18) [10].

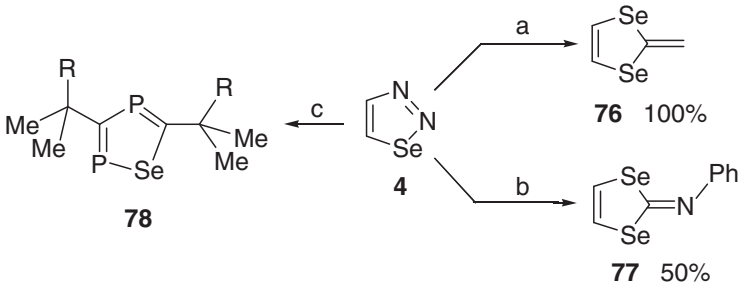
3.4 Ring Transformations

Selenophene and selenium–nitrogen five-membered heterocycles serve as heterodienes in Diels–Alder reactions. [1,4]Cycloaddition at the W/Z positions in **75a** (four atom fragment) is equivalent to [1,3]dipolar cycloaddition in **75b** or **75c**, both providing the 4π-electron component of the cycloaddition (Fig. 7)

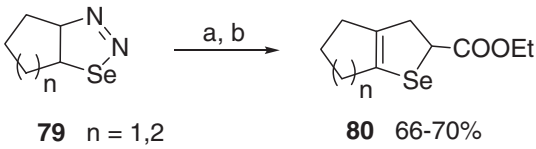
Thermodynamically stable aromatic selenaheterocycles such as selenophene (**1**), 1,3-selenazole (**3**), 1,2,5-selenadiazole (**5**), and 1,2,4-selenadiazole undergo [1,4]cycloaddition followed by spontaneous deselenation, which is a convenient way for construction of nonselenium azaaromatic rings [3, 6, 42]. 3,4-Diphenyl-1,2,5-selenadiazole reacted with DMAD to give methyl 2,3-diphenylpyrazine-5,6-dicarboxylate. The similar reaction of 1,2,4-selenadiazoles resulted in pyrimidine -5,6-dicarboxylate, while 2,1,3-benzoselenadiazoles reacted with DMAD to give the quinoxalines [6, 110]. (For deselenation see also Sect. 5.1).

Cycloadditions to 1,2,3-selenadiazole are followed by extrusion of molecular nitrogen, and nonaromatic selenaheterocycles having a 1,3-diselenole ring (**76**, **77**) [111, 112] or 1,2,4-selenadiphospholes (**78**) are produced (Scheme 19) [113].

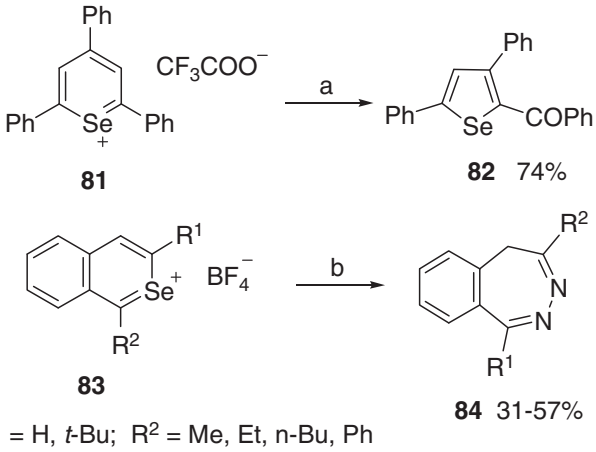
The treatment of 1,2,3-selenadiazoles (**79**) with a catalytic amount of tributyltin hydride and AIBN in the presence of an excess of olefin, gives 2,3-dihydroselenophenes (**80**) in good yield (Scheme 20). The reaction proceeds via tributyltin radical-promoted denitrogenation to give a vinyl radical, which then adds to the olefin followed by intramolecular cyclization. Under similar conditions 1,2,3-selenadiazoles and aliphatic or aromatic ketones afford alkynes as the sole products [114, 115]



Scheme 19 **a** *t*-BuOK, *t*-BuOH, DMF, 20 °C; **b** PhNCSe, *t*-BuOK, *t*-BuOH, DMF, 20 °C; **c** P≡C–CMe_2R, various solvents, 120 °C



Scheme 20 **a** CH_2=CHCOOEt (excess), Bu_3SnH (cat), AIBN; **b** hydroquinone (cat), benzene, 80 °C



Scheme 21 **a** $(AcO)_4Pb$, benzene, 20 °C; **b** H_2N–NH_2, MeCN, 20 °C

Selenaaromatic rings in selenazolium and selenopyrylium salts are transformed to other rings in reactions other then cycloaddition. Examples are: conversion of 1,2,4-selenadiazolium salt (**67**) to 1,3,5-selenadiazine (**68**) (Scheme 17), oxidative ring contraction of selenopyrylium salt (**81**) to selenophene (**82**), or replacement of selenium in the 2-selenachromylium salts (**83**) by two nitrogen atoms resulting in formation of benzodiazepines (**84**) (Scheme 21) [116].

4 Synthesis of Selenaheterocyclic Compounds

4.1 Selenophenes

Selenium analogs of furans and thiophenes have been prepared, replacing the oxygen or the sulfur atom, respectively, in order to improve the bioactivity of these compounds. Furthermore, the polymerization of selenophenes is, by analogy to polythiophenes, of potential technical use. During the last two decades considerable effort has been directed toward synthesis of selenaporphyrins and their macrocyclic analogs having the selenophene ring, the bioactive compounds and metal complexing ligands.

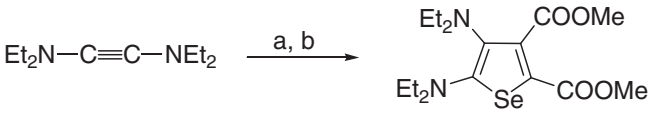
Several reviews are available on the synthesis and properties of selenophene, its derivatives, and compounds having a selenophene ring annulated to benzene or a heterocyclic ring [1, 14, 117–120]. The methods are based on the formation of one, two or three bonds, or on ring transformations.

Among many methods that fall into these categories, the easiest and most studied route is formation of three bonds because it uses acetylene, its derivatives, or 1,3-dienes and inorganic selenium or simple dialkyl selenides.

Selenophene (**1**) is obtained in 30% yield when acetylene reacts with selenium at elevated temperature [121]. Using dimethyl or diethyl diselenide gives higher yields, even above 90% [122, 123]. In the same way, when substituted alkynes are heated with elemental selenium they afford substituted selenophenes [1, 14, 117]. Starting from 1,2-diaminoacetylene (**85**), the tetrasubstituted selenophene (**86**) was obtained even in mild conditions (Scheme 22) [124].

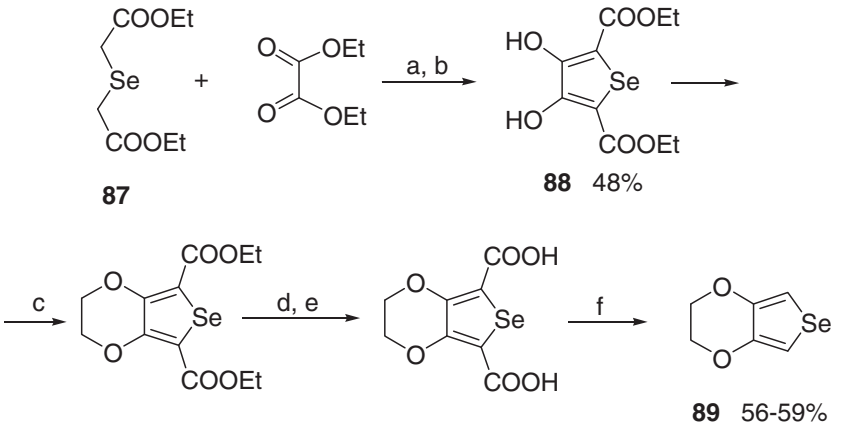
3-Substituted selenophenes were formed in moderate to excellent yields by electrophilic cyclization of (*Z*)-selenoenynes with different electrophiles such as I_2, ICl, PhSeBr, and PhSeCl. The reaction proceeded clearly under mild reaction conditions [125].

2,3,4,5-Tetraphenylselenophene was prepared in high yield from 1,4-diiodo- or 1,4-dilithium-1,2,3,4-tetraphenylbuta-1,3-diene by treatment with dilithium diselenide or diselenium dibromide, respectively [126]. A novel and efficient method for the synthesis of selenophenes from 1,3-dienes containing a carbonyl group at the C-1 position and selenium dioxide has been demonstrated. A cycloaddition-like reaction between dienes and selenium dioxide led to formation of fused selenophenes [127]. A multistep synthesis (outlined in Scheme 23) of the 3,4-ethylenedioxyselenophene



85 **86** 87%

Scheme 22 **a** Se, benzene, 20 °C; **b** MeOOC–C≡C–COOMe, PhCl, 20 °C



Scheme 23 **a** EtONa, EtOH, 20 °C; **b** HCl, H_2O; **c** $BrCH_2CH_2Br$, K_2CO_3, DMF, 110 °C; **d** KOH, EtOH, reflux; **e** HCl, H_2O; **f** Δ

(EDOS, **89**), a novel building block for electron-rich π-conjugated polymers, is based on condensation of diethyl selenodiglycolate (**87**) with diethyl oxalate to tetrasubstituted thiophene (**88**) followed by modification of the hydroxy substituents and decarboxylation [128].

A novel approach to 2,5-diarylselenophenes involved the thermolysis of 1,2,3-selenadiazoles in the presence of excess arylacetylenes [129].

The Suzuki coupling reaction of 2-haloselenophenes with boronic acids catalyzed by palladium salt is a new route to prepare 2-arylselenophenes and 2,5-diarylselenophenes in good yields. In addition, 2-arylselenophenyl ketones were also obtained by this protocol from 2-iodoselenophene and boronic acids via a carbonylative process [130].

The 1-benzoselenophenes are relatively stable and easy to manipulate. Their synthesis has been extensively studied since some of them are analogs of naturally occurring biologically active 1-benzofurans, 1-benzothiophenes, and indoles [1, 14, 118, 120].

The most common methods for the preparation of 1-benzoselenophene and its analogs involve the annulation of the selenophene ring onto a benzene substrate. Early works, such as reaction of selenium with phenylacetylene or the reaction of selenium dioxide with styrene, gave low yields but more recently elaborated procedures, e.g., gas-phase reaction of cinnamaldehyde with dimethyl diselenide at 630 °C, give 1-benzoselenophene in high yield [131, 132].

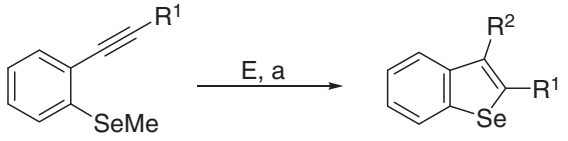
The best direct method for the preparation of 1-benzoselenophenes relies upon the selenenylation of dimetallated 1-arylalk-1-ynes. For example, 1-benzoselenophene was prepared in this manner by reaction of selenium with dilithiated phenylacetylene followed by the addition of *t*-butyl alcohol and HMPA to the reaction mixture [133, 134].

The reaction of 1-alkynyl-2-bromobenzenes with elemental selenium is a general one-pot method for the synthesis of 2-substituted 1-benzoselenophenes [135, 136]. The reaction of 1-arylalk-1-ynes with selenium dioxide in the presence of hydrogen halides leads to the corresponding 1-benzoselenophenes in reasonable to poor yields [137, 138]. The addition of selenium tetrachloride or tetrabromide to 1-alkyl-1-ynes gave 3-halo- and 2,3-dihalo 1-benzoselenophenes, depending upon the number of equivalents of reagent employed [119, 139].

New substituted selenophenes were prepared from ketene dithioacetals. Isoselenocyanates were used to obtain aminoselenophenes. Starting from substituted methylsulfonylselenophenes, thieno- and selenolo-selenophenes were synthesized [140].

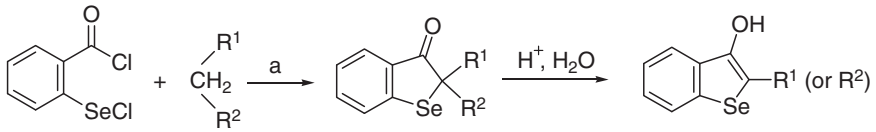
An expedient method for synthesis of 2,3-disubstituted 1-benzoselenophenes (**91**) by the electrophilic cyclization of various 1-(1-alkynyl)-2-(methylseleno)arenes (**90**) has been reported recently (Scheme 24). This method tolerates a wide of variety of functional groups, and proceeds under exceptionally mild reaction conditions [141]. Moreover, an efficient solid phase synthesis of **91** based on a combination of palladium-mediated coupling and iodocyclization protocols has been developed [142].

A unique synthesis of 1-benzoselenophenones (**93**) and 3-hydroxy-1-benzoselenophenes (**94**) relies upon tandem selenenylation–acylation of the activated methylene groups by 2-(chloroseleno)benzoyl chloride (**92**) (Scheme 25). When acylacetones were used as the substrates, initially formed **93** underwent deacylation to 3-hydroxy derivatives **94** [47, 48].



90 **91** 43-98%

Scheme 24 **a** CH_2Cl_2, 20 °C; E = Br_2, NBS, I_2, ICl, PhSeCl, PhSeBr, $Hg(OAc)_2$; R^1 = aryl, alkyl, alkenyl; R^2 = I, Br, PhSe



92 **93** 31-78% **94** 12-100%

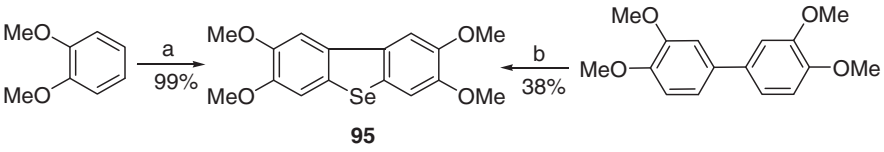
Scheme 25 **a** Et_3N, CH_3COOEt, −15 °C or 20 °C.; R^1 = H, CN, COOMe, COOEt; R^2 = COMe, COPh, COOEt, 4-NCC_6H_4, $CO(4\text{-}BrC_6H_4)$, $CO(4\text{-}BrC_6H_4)$, $P(O)(OEt)_2$; R^1–R^2 = $CO(CH_2)_2CO$, $CO(CH_2)_3CO$

By far the most common methods for the preparation of dibenzoselenophenes and 2-benzoselenophenes, like the synthesis of 1-benzoselenophenes, rely upon the annulation of the heterocyclic ring system onto a preformed benzene ring and mostly involve the formation of one or two Se–C bonds as their key steps, with only a few exceptions [1, 119, 120]. Intramolecular electrophilic aromatic substitution of biphenyl-2-yl trifluoromethylselenide to 5-(trifluoromethyl)dibenzoselenopheni um triflate (**62**) [99, 143] and synthesis of tetramethoxydibenzoselenophene (**95**) (Scheme 26) [144, 145] are examples.

In common with related heterocycles, 2-benzoselenophene is unstable and cannot be isolated but can be stored in solution and easily undergoes the Diels–Alder reaction [146]. In contrast, the 1,3-disubstituted 2-benzoselenophenes are stable compounds and synthesis of 1,3-dicyano 2-benzoselenophene (**97**) starting from *o*-xylene dicyanide (**96**) using $SeOCl_2$ as selenium transfer reagent was reported (Scheme 27) [147].

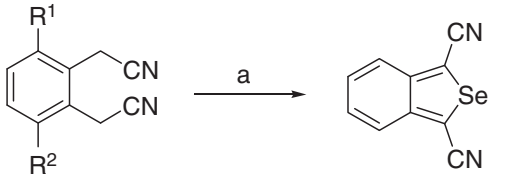
For the first time, the synthesis of a range of 1,3-diaryl-2-benzoselenophenes has been achieved involving a selenium transfer reaction of 1,3-diaryl-2-benzofuran using Woolins reagent $[PhP(Se)(\mu\text{-}Se)]_2$, a selenium analog of the well-known sulfur transfer Lawesson reagent [148].

The unstable selenolo[2,3-*b*]quinoxaline was generated and functionalized in situ to give the stable 1,3-dialdehyde and 1,3-diester derivatives. The 1,3-dicyanoselenolo[2,3-*b*]quinoxaline was made in several steps from biscyanomethyl selenide and was found to be a very stable compound [149].



95

Scheme 26 **a** $MeSeSO_3^- NH_4^+$ (5 eq); **b** $SeCl_2$, AcOH, 120 °C



96 **97** 10%, 50%

Scheme 27 **a** LDA, $SeOCl_2$, −78 °C then 20 °C $R^1 = R^2 = H$; $R^1 = Cl$, $R^2 = Br$

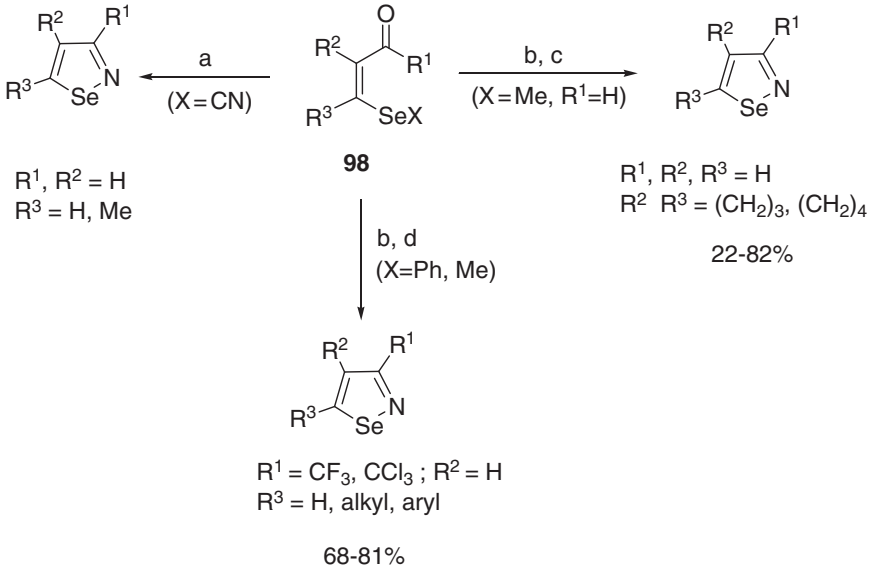
4.2 1,2-Selenazoles

The most commonly used method for synthesis of 1,2-selenazoles (isoselenazoles) is addition of ammonia to 3-selenosubstituted enones such as **98** (Scheme 28) [2, 10, 150, 151].

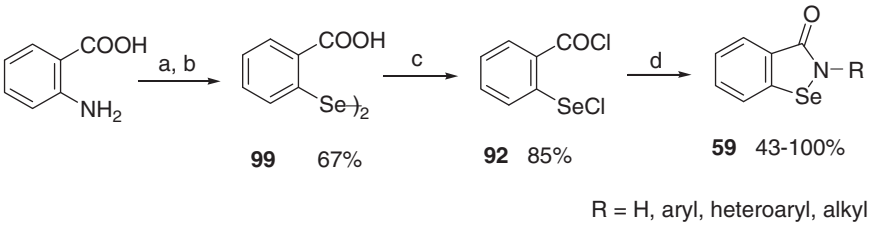
1-Benzo-1,2-selenazoles (1-benzisoselenazoles) were prepared in a similar manner to 1,2-selenazoles, by the addition of bromine followed by ammonia to 2-(methylselanyl)benzaldehydes or by the alternative methods referred to in the reviews [2, 10, 74].

Because of growing interest in their nonconjugated analogs, the 1-benzo-1,2-selenazol-3(*2H*)-ones (commonly named benzisoselenazol-3(*2H*)-ones) (**59**), as bioactive species and oxygen transfer agents a number of papers have dealt with their synthesis. The earliest and the most versatile approach to preparing **59**, particularly 2-phenylbenzisoselenazol-3(*2H*)-one (named ebselen) was obtained from the 2-(chloroseleno)benzoyl chloride (**92**) and primary amines [152]. In the meantime, the procedure was modified and optimized. The dichloride (**92**) was obtained from anthranilic acid by diazotization and replacement of the diazonium group by a diselenide group, followed by treatment of intermediate 2-(carboxy)phenyl diselenide (**99**) with a large excess of the thionyl chloride [92, 153–156] (Scheme 29).

This strategy was employed for the synthesis of a broad spectrum of **59** having, at the 2-position, hydroxyalkyl, hydroxyaryl, carboxyalkyl, thioalkyl, acyl,



Scheme 28 **a** Liq. NH_3, **b** Br_2, CH_2Cl_2, –80 °C; **c** NH_3, 20 °C; **d** NH_3, –70 °C



Scheme 29 **a** $NaNO_2$, HCl, H_2O; **b** Na_2Se_2; **c** $SOCl_2$, DMF (cat), reflux; **d** RNH_2, CH_2Cl_2, 20 °C

sulfonyl, and other substituents [50, 153, 155–157]. Following this procedure, the ^{75}Se-labeled, spin-labeled, and other paramagnetic benzisoselenazol-3(*2H*)-ones, organoselenium-modified sugars, β-cyclodextrins, and adenosine were obtained [158–162]. 2-(Phosphonoalkylamino)-benzisoselenazol-3(*2H*)-ones were prepared by reaction of dichloride (**92**) with 1-hydrazinophosphonates [163], while cyclocondensation with α -aminophosphonates gave 2-(phosphonoalkyl)benzisosele nazol-3(*2H*)-ones [164].

Bisbenzisoselenazol-3(*2H*)-ones having both heterocyclic moieties bridged by spacers such as phenylene, bisphenylene, alkylene, oxaalkylene, azaalkylene, and dithiaalkylenes were obtained from the reaction of **92** with corresponding compounds having two primary amino groups [156]. Some of the benzisoselenazol-3(*2H*)-ones were covalently bound to the silica or polymer support [18, 165]. Novel porphyrins bearing the 2-phenylbenzisoselenazol-3(*2H*)-one moiety were synthesized and characterized [166].

2-(Chloroseleno)nicotinyl chloride treated with primary aliphatic or aromatic amines gave 2-substituted 7-azabenzisoselenazol-3(*2H*)-ones [51].

Another preparative route for synthesis of benzisoselenazol-3(*2H*)-ones is based on the lithiation of the benzamides, followed by the conversion of dilithium derivatives by direct treatment with selenium, or via 2-[(carbamoyl)phenyl]methyl selenides or 2,2′-bis[(carbamoyl)phenyl] diselenides [167–172]. These diselenides are oxidatively cyclized and, depending on the oxidant used, benzisoselenazol-3 (*2H*)-ones or their 1-oxides are produced in high yields [92, 173].

4.3 1,3-Selenazoles

The synthesis and properties of 1,3-selenazoles and annulated 1,3-selenazole compounds have been the subject of numerous reviews, e.g., [3, 14, 34, 174, 175]. The pure parent selenazole was obtained, only in a low yield, by reaction of selenoformamide with α-chloro or α-bromoacetaldehyde [174, 176].

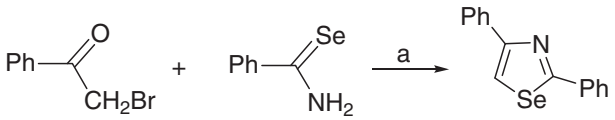
Condensation of selenocarboxamides with α-chloro- or α-bromocarbonyl compounds gives access to a wide variety of substituted 1,3-selenazoles by choosing suitable reaction partners and, in most cases, they are produced in good to excellent yields [3, 14, 174]. For example, the phenacetyl bromide (**100**) and selenobenzamide (**101**) gave 2,4-diphenyl-1,3-selenazole (**102**) (Scheme 30) [174].

An important modification is reaction of β-dicarbonyl compounds with [hydrox y(tosyloxy)iodo]benzene and selenourea as a one-pot synthesis [177]. Similarly, α-tosyloxylation of acetophenones, cyclohexanone, or pentan-3-one with the same reagent, followed by treatment with arylselenobenzamides, gives 2,4-disubstituted and 2,4,5-trisubstituted 1,3-selenazoles [178].

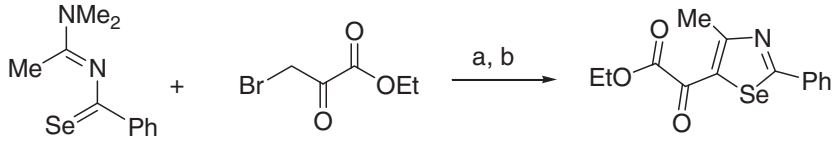
Treatment of *N*-[1-(dimethylamino)ethylidene]benzenecarboselenoamide (**103**) with ethyl bromopyruvate in the presence of triethylamine affords 5-[(ethoxy carbonyl)acetyl]-4-methyl-2-phenyl-1,3-selenazole (**104**) (Scheme 31) [179]. In a similar reaction of morpholino(selenocarbonyl)-amidines with 2-(chloromethyl)-5-nitrothiophene other substituted 1,3-selenazoles were obtained [180].

The reaction of isocyanides with organolithium reagent affords α-lithiated isocyanides (**105**), which react with isoselenocyanates to give ambident anions (**106**) (Scheme 32). Then the selenium atom attacks intramolecularly at the carbon atom of the isocyanide moiety to give 4,5-dihydro-1,3-selenazole derivatives (**107**). The aromatization of **107** to **108**, followed by protonation, affords 1,3-selenazoles (**109**) [181].

A convenient route to the 1,3-selenazole nucleus uses a polyfunctional reagent such as the vinylphosphonium salt (**110**), which with sodium hydrogen selenide gives the ylide (**111**) (Scheme 33). Cyclization of (**111**) yields the phosphonium derivative (**112**). A variety of compounds have been prepared by this method [182–184].

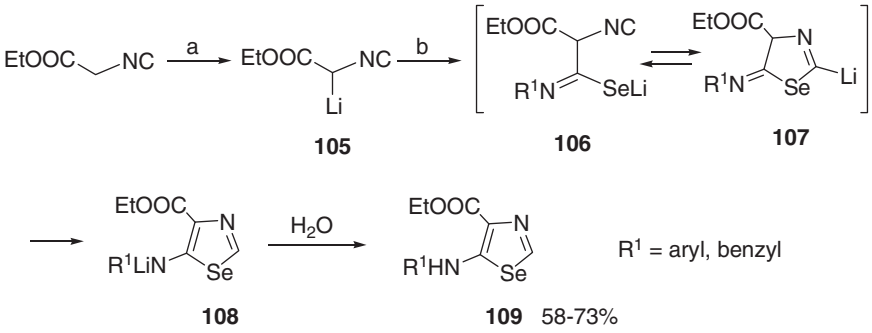


Scheme 30 **a** H_2O, 20 °C **100** **101** **102** 87%

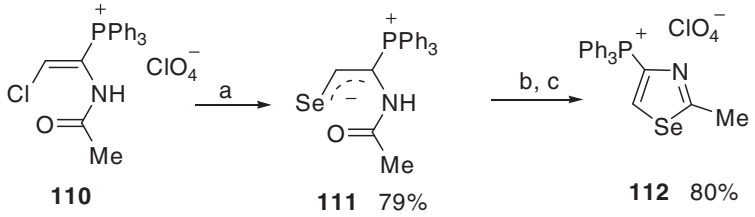


103 **104** 55%

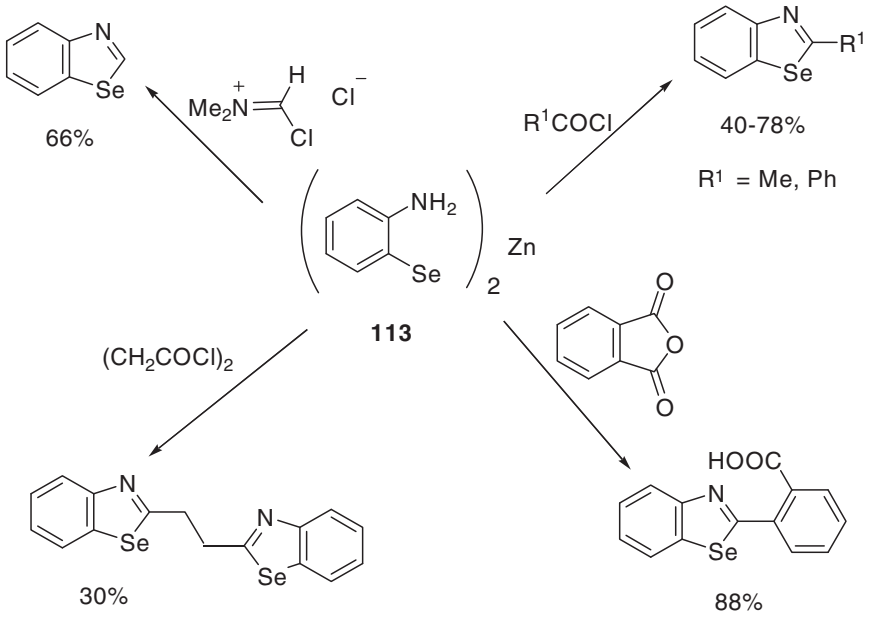
Scheme 31 **a** CH_2Cl_2, 20 °C; **b** Et_3N, 20 °C



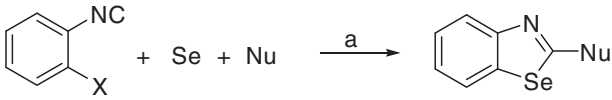
Scheme 32 **a** LHMDS, BuLi, hexane, THF, HMPA, −70 °C; **b** RNCSe, −70 then 20 °C



Scheme 33 **a** NaSeH (excess); **b** HCl; **c** $HClO_4$



Scheme 34 Preparation of benzoselenazoles



114 **115** 48-99%

Scheme 35 **a** CuI, DBU, THF, 20 °C X = Br, I; Nu = R^1R^2NH, ROH, RSH

The traditional and most general method of preparing benzoselenazoles has been to react the *o*-aminophenylselenate as zinc salt (**113**) with acylating agents (Scheme 34) [3, 175]. By using the *N*,*N*-dimethylchloroiminium chloride, unsubstituted 1-benzo-1,3-selenazole was obtained [185]. 2-Aryl-7-aza-1-benzo-1,3-selenazole can be prepared from lithiated 2-chloro-3-aminopyridine by reaction with arylselenoesters ArC(Se)OEt [186].

A simple and practical useful synthetic method for 1-benzo-1,3-selenazoles (**115**) having a heteroatom substituent such as NR^1R^2, OR, or SR groups at the 2-position was developed by the copper(I)-catalyzed reaction of isocyanides (**114**) with selenium and heteroatom nucleophiles (Scheme 35) [187].

4.4 Selenadiazoles

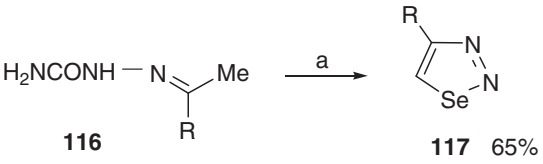
Many 1,2,3-selenadiazoles have been prepared as intermediates for the ultimate preparation of other organic compounds or for biological activity evaluation [6]. The most general, extensively applied method is based on the oxidation of semicarbazones, mostly derived from aromatic and carbocyclic ketones, by selenium dioxide [6, 14, 188–191]. Synthesis of 4-(2-naphthyl)-1,2,3-selenazole (**117**) from semicarbazone (**116**) is an example (Scheme 36).

Symmetrically substituted 1,2,4-selenadiazoles (**119**) are obtained by oxidation of primary selenoamides (**118**) with NBS (Scheme 37) [192] or with Na_2PdCl_4, diacetoxyiodobenzene, or iodosoacetate [193, 194]. Treatment of selenobenzamides with benzenesulfonyl-2-bromo-1-phenylethane leads to 1,2,4-selenadiazoles having different substituents at the 3 and 5 positions [195].

Only a few works on the synthesis of 1,3,4- and 1,2,5-diazoles have been reported, all in older literature [6, 14]. More attention has been paid to synthesis of benzo-2,1,3-selenadiazoles simply obtained by reaction of aromatic or heteroaromatic 1,2-diamines with selenium dioxide [196–199].

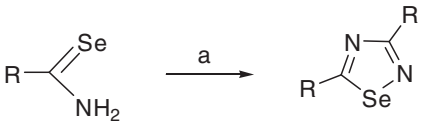
4.5 Selenaporphyrins

The porphyrins are called “pigments of life” and occur broadly in nature. They fulfill many roles ranging from oxygen transportation (hemoglobin), electron transfer (cytochromes), oxidations and reductions (peroxidase, catalase, cytochrome, oxi-



116 **117** 65%

Scheme 36 **a** SeO_2, AcOH, Δ R = 2-naphthyl



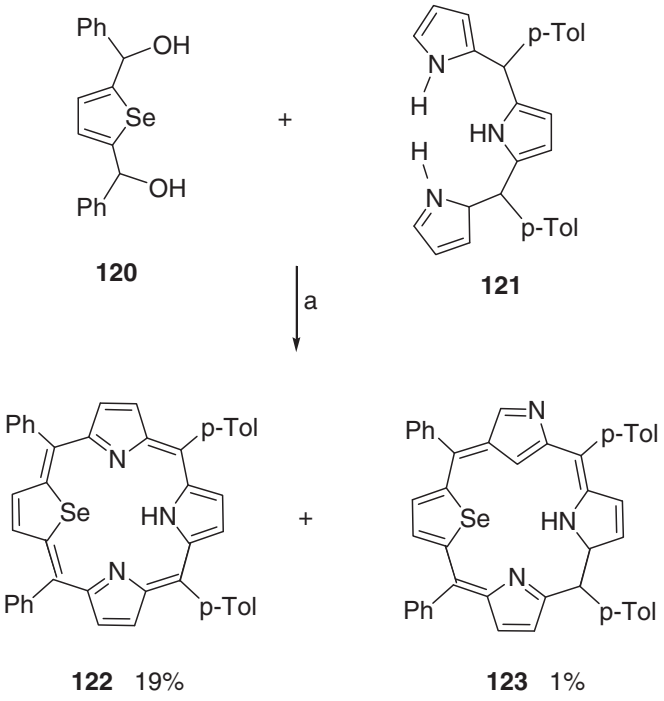
118 **119** 32-87%

R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, $MeCH_2CH_2$, $Me(CH_2)_3CH_2$, $Me(CH_2)_5CH_2$, Me_2N, $PhCH_2S$

Scheme 37 **a** NBS, $CHCl_3$, 20 °C

dase), to light harvesting and photosynthesis (chlorophylls). Although naturally ocurring porphyrins have no chalcogen atoms in the macrocycle ring, many efforts have been made to synthesize modified and expanded porphyrins. Among these have been the porphyrins and analogs modified by introduction of selenium atoms. Synthetic porphyrins have been investigated for numerous applications, including the production of molecular wires, oxidation catalysts, novel optical materials, and components of molecular-based information storage systems, as well as photosensitiziers in photodynamic therapy. The growth of interest in analogs of the porphyrins and also in selenaporphyrins, selenasaphyrins, and selenaheptaphyrins is due to the expectation that these systems will also possess useful applications. Some effort has been devoted to the systematic developments of macrocyclic systems where modification of porphyrin has been achieved by introduction of other donors (O, S, Se, NCH_3, NO, N–C–, CH) to replace or modify one of the pyrrole nitrogens [70, 71, 200–209]. The porphyrins containing one or two selenium atoms in the macrocyclic ring as well as core-modified expanded selenaporphyrins were obtained by the acid-catalyzed condensation of pyrrole (**121**) with bis(phenylhydro xymethyl)selenophene (**120**) [70, 71, 206, 210–212]. For example, 5,20-diphenyl-10,15-bis(*p*-tolyl)-21-selenaporphyrin (**122**) and its isomer (**123**) with an inverted pyrrole ring was obtained by a [3 + 1] condensation of (**120**) and 5,10-ditolyltripyrrin (**121**) (Scheme 38) [210].

Remarkably, the acid catalyzed condensation of 16-selenatripyrrane gave 18-π, 22-π, and 26-π macrocycles (*meso*-aryldiselenaporphyrins, diselenasaphyrins, and



Scheme 38 **a** $BF_3{\cdot}Et_2O$, chloranil, CH_2Cl_2, 20 °C then reflux

diselenarubyrins), respectively [213, 214]. The formation of diselenasaphyrin and diselenaporphyrin requires fragmentation of tripyrranes followed by condensation of the formed moieties [214].

4.6 Seleninium Salts

The best known selenaaromatic ionic systems are seleninium salts having a selenium atom placed in a six-membered ring. The synthesis and chemistry of selenopyrylium, 1-benzo-, 2-benzo- and dibenzoselenopyrylium salts have been extensively studied since the applications of these compounds in medicine and material chemistry [7, 215, 216]. Very few general methods exist for the synthesis of selenopyrylium salts from acyclic precursors. The majority of the methods that are most commonly employed rely on the formation of the salts from another heterocyclic system by either an elimination process or by an aromatization.

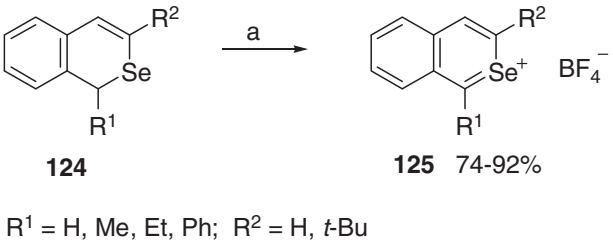
The most general method for the formation of selenopyrylium salts from acyclic precursors involves the reaction of 1,5-diketones with a dibasic source of selenium, mainly hydrogen selenide, or by reaction of the 5-chloropenta-2,4-

dienenitriles with sodium hydrogen selenide. The methods are limited mainly by the poor yields [216].

The aromatization of selenopyrans is an excellent method for preparation of the corresponding selenopyrylium salts. The procedure is simple and the yields are high. A variety of reagents have been employed to bring about the oxidation step including triphenylcarbenium tetrafluoroborate, as shown for conversion of isoselenochromenes (**124**) to 2-benzoselenopyrylium tetrafluoroborates (**125**) (Scheme 39) [216–221]. Other reagents include a combination of bromine and carbon tetrabromine in the presence of ultraviolet light [83, 222]. Oxidation of selenopyrans with 3,5-di-*tert*-butyl-benzo-1,2-quinone gave selenopyrylium salts in high yields [223].

One of the most versatile methods for the synthesis of selenopyrylium salts involves dehydration of 4-hydroxyselenopyrans, or their benzoannulated analogs, which are generated from the corresponding selenopyranon-4-ones by either reduction ($LiAlH_4$, MeLi) or by the additions of Grignard reagent. For example, treatment of selenopyranone (**126**) with methylmagnesium bromide give intermediate 4-methyl-4-hydroxyselenopyrane (**127**), which on treatment with hexafluorophosphoric acid, eliminate water to give selenopyrylium salt (**128**) in excellent yield (Scheme 40) [224, 225].

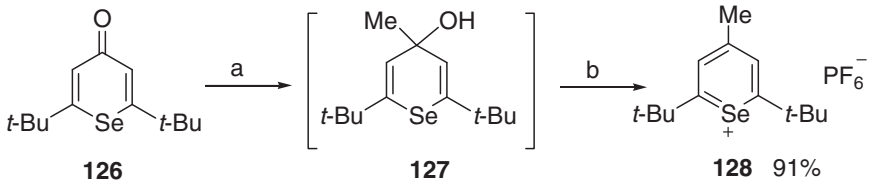
Using similar methodology, 2,4,6-triarylselenopyrylium hexafluorophosphates were obtained and evaluated as in-vivo sensitizers for photodynamic therapy of cancer [226–229].



124 **125** 74-92%

R^1 = H, Me, Et, Ph; R^2 = H, *t*-Bu

Scheme 39 **a** $Ph_3C^+ BF_4^-$, $MeNO_2$, 20 °C



126 **127** **128** 91%

Scheme 40 **a** MeMgBr, THF, Et_2O, Δ; **b** HPF_6

5 Selenaheterocyclic Compounds of Practical Importance

5.1 Reagents and Catalysts for Organic Synthesis

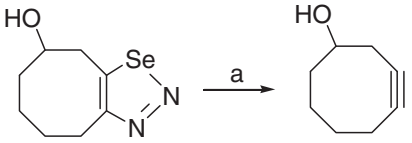
During the last decade, the long-standing but modest use of selenium reagents by organic synthetic chemists received a new impetus. Among the numerous organoselenium reagents, catalysts, and intermediates employed in synthesis, some were heterocyclic but only a few were heteroaromatic. Nevertheless, their role, in some synthetically useful reactions for preparation of nonselenium organic compounds is prominent and worthy of note. The reactions can be divided into two groups: (i) those which proceed through extrusion of the selenium in thermal or reductive conditions, or under treatment with a nucleophile (photochemical extrusion of the selenium is of minor importance for use in synthesis), and (ii) those where selenium plays a role as oxygen-transfer agent.

The ready thermal and photochemical decomposition of 1,2,3-selenadiazoles resulting in extrusion of nitrogen and selenium or nitrogen only has been exploited widely in synthesis from more than 30 years. Their thermolysis or decomposition with butyllithium gave the alkynes. More recently, thermolysis of 1,2,3-selenadiazoles fused to carbocyclic rings, e.g., **129** was used for synthesis of cycloalkynes such as **130** (Scheme 41) [6, 230–232].

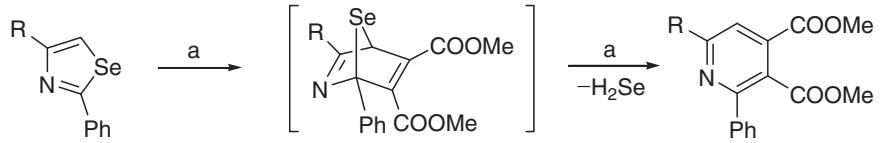
The valuable synthetic intermediates are benzo-2,1,3-selenadiazoles. They were used for preparation of *N*-alkyl-1,2-benzenediamines, 3-nitro-1,2-benzenediamines, 3,4-diamino-2-nitrophenols, and 5-nitroqunoxalines. The key step of the reaction is their reductive deselenation with hydrogen iodide or, better, with ammonium hydrosulfide [233–238].

Selenazole and the 1,2,4- and 1,2,5-selenadiazoles serve as heterodienes in the Diels–Alder reaction. [1,4]Cycloaddition of the active dienophiles to these selenaheterocyclic compounds, followed by deselenation, is a convenient means of synthesis of a nonselenium azaaromatic ring. Cycloaddition of 2,4-disubstituted 1,3-selenazole (**131**) with DMAD forms a bicyclo intermediate (**132**) that undergo extrusion of elemental selenium liberating the pyridine product (**133**) (Scheme 42) [110].

3,5-Disubstituted 1,2,4-selenadiazoles reacted with DMAD with extrusion of selenium to give pyrimidine-5,6-dicarboxylates, while 1,2,5-selenadiazoles produce pyrazines. In a similar way, quinoxaline can be obtained from benzo-2,1,3-selenadiazoles [6, 110]. (For deselenation see also Sect. 3.4).



Scheme 41 **a** Cu, Δ **129** **130** 34%



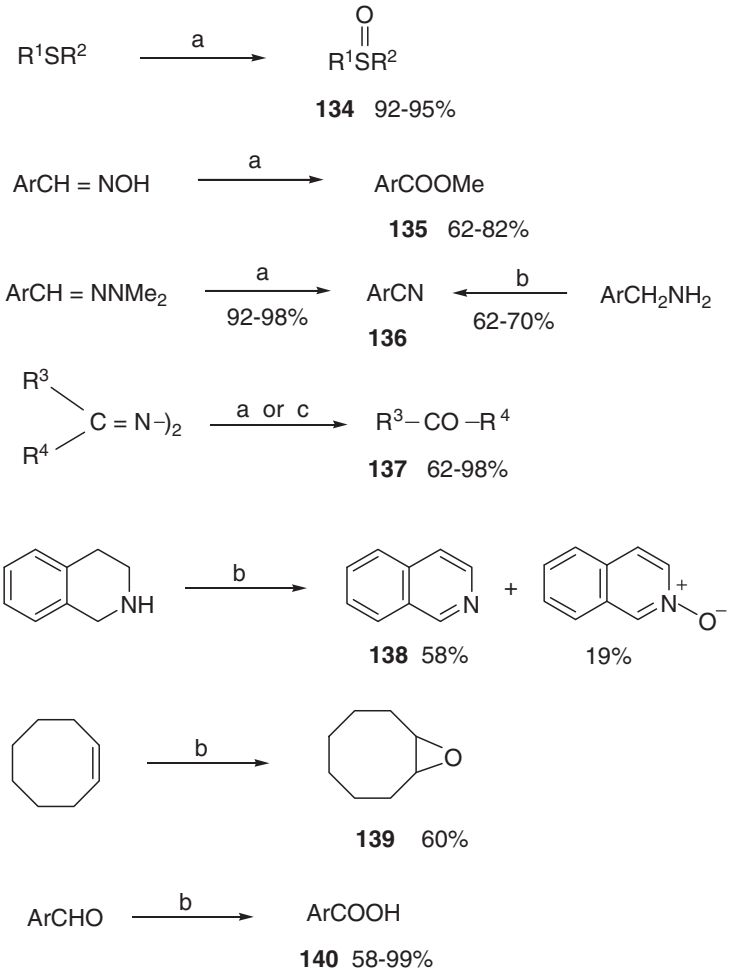
131 **132** **133** 41-55%

Scheme 42 **a** DMAD, benzene, 150 °C

The methyl selenienyl salt (**62**, Y = CH_3) (Fig. 6), readily obtained from dibenzoselenophene, is a powerful methylation agent even in water as a solvent. Its trifluoromethyl analogue (**62**, Y = CF_3) can be used as a trifluoromethylating electrophile, although the sulfur analog is more reactive [98, 99]. 2-Benzoselenopyrylium salts (**83**) were used in preparation of benzodiazepines (**84**) (Scheme 21) by treatment with hydrazine [116].

Selenium(IV) oxide and nonheterocyclic organoselenium compounds have been employed as stoichiometric oxidants or oxygen-transfer agents used in catalytic amounts. An attractive approach is based on the use of organoselenium compounds when the stoichiometric oxidant is 30% aqueous hydrogen peroxide or 80% *tert*-butyl hydroperoxide (TBHP). For many reactions, benzisoselenazol-3(*2H*)-ones, particularly ebselen (**59**, R = Ph) used in 5% molar amount (related to the substrate), were found to be the most versatile oxygen-transfer catalysts among organoselenium compounds. Synthetically useful reactions catalyzed by ebselen (Scheme 43), where the stoichiometric oxidants are environmentally neutral hydrogen peroxide or TBHP, are: selective oxidation of sulfides to sulfoxides (**134**) [239], oxidation of oximes in the presence of primary or secondary alcohols to esters (**135**) [240], oxidative conversion of *N*,*N*-dimethylhydrazones or benzylamines into nitriles (**136**) [241, 242], regeneration of the parent ketones (**137**) from azines [240], dehydrogenation of tetrahydroisoquinoline to isoquinoline (**138**) [242], oxidation of cyclooctene to epoxide (**139**) [243], and oxidation of aromatic aldehydes to arenecarboxylic acids (**140**) with avoiding of the Baeyer–Villiger rearrangement [93]. All these reactions have practical value since procedures are simple and the products can be isolated in high to excellent yields. The reaction conditions and the results suggest the ionic mechanism.

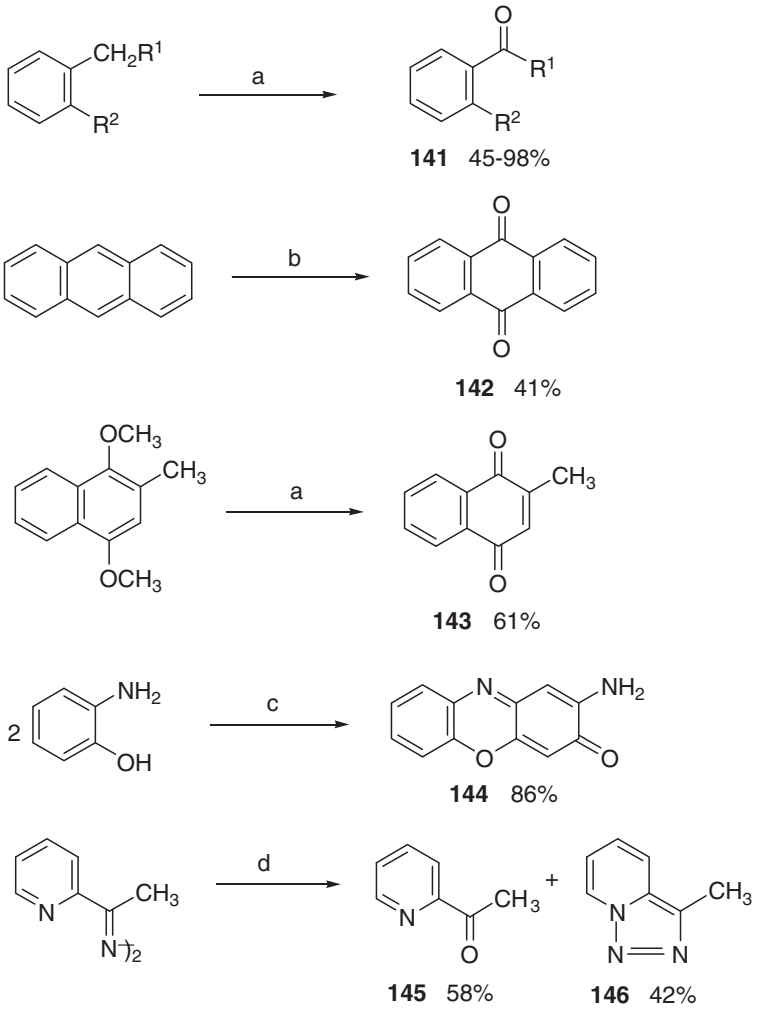
Despite the ionic reactions, other reactions (presented in Scheme 44) show that free-radical mechanisms can also take place. Catalyzed by ebselen, TBHP oxidation of alkylarenes to alkyl aryl ketones (**141**) [240], anthracene to anthraquinone (**142**), 1,4-dimethoxyarenes to 1,4-quinones (e.g., menadione **143**) [244], and oxidative coupling of 2-aminophenol to phenoxazinone (**144**) [245] gave results similar to these when one-electron oxidants such as Ce(IV), Ag(II), or Mn(III) were the reagents. Moreover, oxidation of azine derived from 2-acetylpyridine gave a mixture of ketone (**145**) and condensed triazole (**146**) [240]. The same result was found when cerium ammonium nitrate was used as the reagent. This suggests that the



Scheme 43 **a** H_2O_2, ebselen (cat.), MeOH, 20 °C; **b** TBHP, ebselen (cat.), *t*-BuOH, reflux; **c** H_2O_2, ebselen (cat.), MeOH, 65 °C

reaction proceeds via cation-radicals. Both of the postulated mechanisms, ionic and free radical, were discussed in more detail in a review article [16].

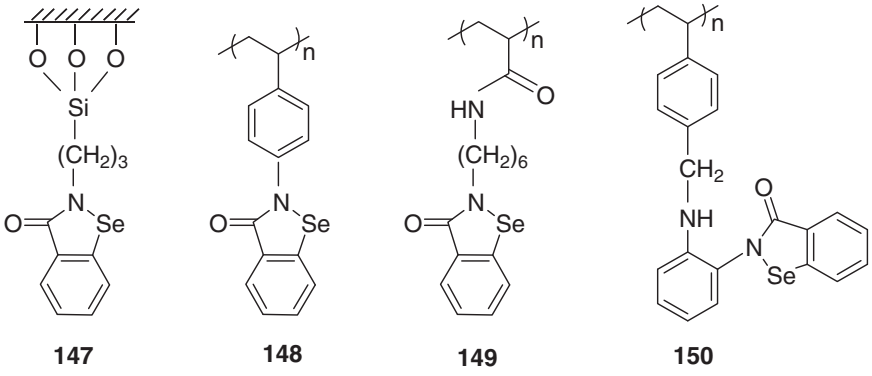
A few benzisoselenazol-3(2*H*)-ones were covalently immobilized to the solid support, either silica [165] or polymer [246] (**147**–**150**) (Fig. 8). They exhibited appreciable catalytic activity similar to the activity of ebselen. The most interesting prospective oxygen-transfer catalyst is benzisoselenazolone covalently bound to a silica support (**147**) named HALICAT. It has been applied to hydrogen peroxide oxidation of the sulfides and TBHP oxidation of the aromatic aldehydes and alkylarenes. The catalyst can be easily filtered off from the mixture after the reaction and reused several times [165].



Scheme 44 **a** TBHP, ebselen (cat.), *t*-BuOH, reflux; **b** TBHP, ebselen (cat.), MeCN, reflux; **c** H_2O_2, ebselen (cat.), *t*-BuOH, 20 °C; **d** H_2O_2, ebselen (cat.), MeOH, reflux

5.2 Bioactive Compounds

The biochemistry and pharmacology of selenium compounds, among them aromatic selenaheterocycles and their nonconjugated analogs, are subjects of intense current interest, especially from the point of view of public health. During the last few years, a tremendous effort has been directed toward the synthesis of stable organoselenium compounds that could be used as antioxidants, enzyme modulators, antitumors, antivirals, antimicrobials, antihypertensive agents, and cytokine



147 **148** **149** **150**

Fig. 8 Benzisoselenazol-3(2*H*)-ones covalently immobilized on the solid supports

inducers. Their possible applications as therapeutic agents in treatment of several diseases has been revealed in numerous papers and recently discussed in the reviews [18–21, 247]. Because of growing interest in the bioactive selenaaromatic compounds and their nonaromatic analogs both of these groups will be briefly presented in this section.

Reactive oxygen species such as the hydroxyl radical, superoxide anion, and peroxynitrite are involved in many cellular processes including the inflammatory response. The best known antiinflammatory compound is ebselen (**59**, R = Ph). It is shown to be a neuroprotective agent and an inhibitor of free radical-induced apoptosis [20, 248, 249]. It has undergone phase III clinical trials and is soon to become the first synthetic organoselenium therapeutic released on the market.

Ebselen acts as a GP_x mimic by reducing hydroperoxides to water or the corresponding alcohol, and a mechanism involving oxidation of thiols to the disulfides has been postulated [20].

More recently, it has been demonstrated that ebselen is also able to catalytically reduce hydroperoxides through reaction with the thioreductase (Trx) system [247, 250]. Inflammatory enzymes, known as the lipoxygenases (LOX) and cyclooxygenases (COX), activated by hydroperoxides, are attractive targets for inhibition in the pursuit of antiinflammatories such as ebselen and others. The capacity for ebselen to act as LOX inhibitor is critical to its antiinflammatory activity. The inhibition of LOX by ebselen may be a result of its antioxidant activity or through its direct interaction with the enzyme [247].

The activity of ebselen can be altered by modifying its structure. Substitution of the hydrogen atom of the benzene ring with a nitro group in the *ortho*-position to selenium has been shown to increase of the GP_x activity of ebselen. The sulfur analog of ebselen and the compounds having no Se–N bond in the ring are inactive [18, 20, 247].

It has been postulated that cleavage of the Se–N bond is responsible for the biological activity of benzisoselenazol-3(2*H*)-ones and several research groups

have prepared different compounds having a selenenamide moiety in the heterocyclic ring [20, 21, 251–255]. The camphor-derived cyclic selenenamide (**151**), selenenamides (**152**, **153**) having a supplementary tetrahedral carbon in the ring (Fig. 9), and the compound **154**, with an annulated 1,2,3-selenadiazole ring, all display appreciable GP_x mimetic activity. The compound **153** has been in clinical development as a drug candidate for the treatment of ulcerative colitis. Moreover, selenaheterocyclic compounds having labile Se–O instead of the Se–N bond (such as cyclic seleninate esters like **155** and spirodeoxyselenuranes like **156**) were evaluated as GP_x mimetics and their antioxidant activity was higher than that of ebselen [256].

The efficacy of ebselen is somewhat limited by its low water solubility. In the pursuit of preparing GP_x mimics, β-cyclodextrins with an ebselen moiety tethered to the primary ring were obtained. These compounds had excellent solubility in water and cyclodextrin (**157**) displayed GP_x activity on par with that of ebselen [162, 257, 258].

Ebselen and related compounds, among them carboxylated analog **59** (R = 4–C_6H_4COOH), have been reported to be inhibitors of constitutive endothelial nitric oxide synthase (ec NOS) [153, 258–260]. Selenourea derivatives, among them 2-aminoselenazoline, are potent inhibitors of the iNOS [261].

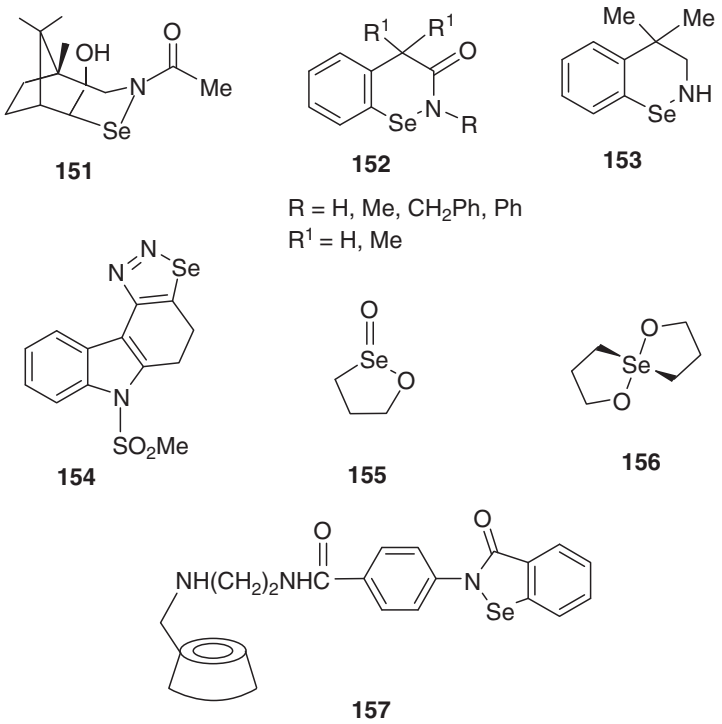


Fig. 9 Cyclic selenenamides, seleninate ester and spirodeoxyselenurane

Selenazofurin (**158**), selenophenfurin (**159**), and dinucleosides such as **160** (Fig. 10), are potent inosine monophosphate dehydrogenase (IMPDH) inhibitors and have pronounced antitumor activity in animals and broad spectrum antiviral as well as maturation-inducing activities [262–264]. The inhibitory effects of heterocyclic organoselenium compounds such as ebselen and some of its derivatives have been demonstrated on 15-LOXs [21, 265].

Despite very promising research, to date no synthetic organoselenium compounds are in clinical use as anticancer agents. The applicability of selenaheterocyclic compounds in tumor control has been demonstrated in five-membered ring systems. The search for novel antitumor agents resulted in the successful development of the three prospective compounds (**161–163**) (Fig. 11) that were tested against tumor growth in a mouse model. They markedly inhibited the growth of

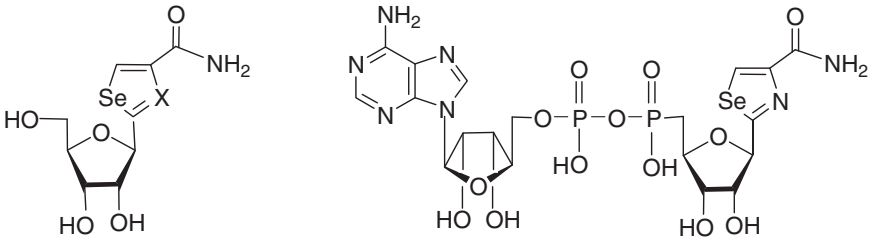


Fig. 10 Selenium nicotinamide adenine dinucleoside (NAD) analogs

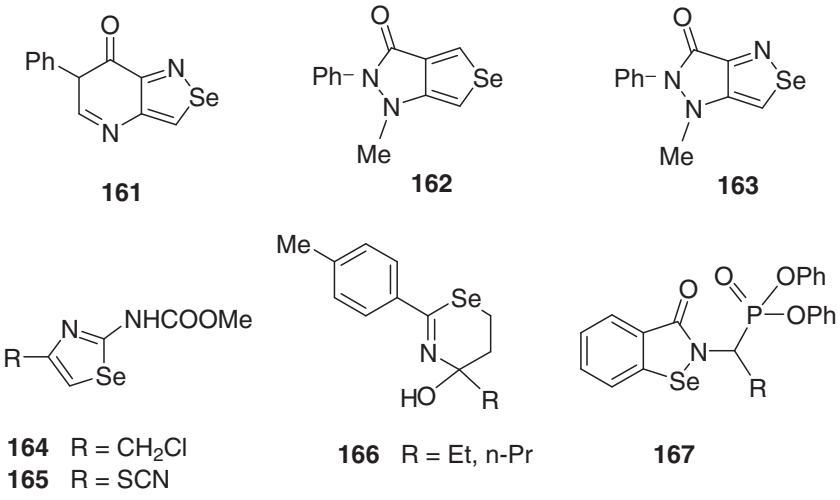


Fig. 11 Antitumor selenaheterocycles

P388 mouse leukemia at a dose of 100 μg/mouse/day without exhibiting any toxicity [266]. 2,4-Disubstituted 1,3-selenazoles (**164**, **165**), evaluated for their antitumor activity by determining their ability to inhibit proliferation of L1210 cells in vitro, exhibited appreciable activity, although the 1,3-selenazole (**165**) was less potent than the sulfur analog [267, 268].

A number of 1,3-selenazole and 1,3-selenazine derivatives have been reported as antiproliferative agents. The most active against human fibrosarcoma HT-1080 cells were 1,3-selenazines (**166**) [269]. Further, certain 2-phosphonoalkylbenzisoselenazol-3(2*H*)-ones (**167**) were synthesized and their potent activity against human carcinoma cells in vitro was reported [164].

Selenium-containing virucides, usually in the form of nucleoside synthetase inhibitors, are selenazofurin (**158**) and oxaselenolane nucleoside (**168**) [21, 247, 270]. While bearing a broad spectrum of antiviral activity, unfortunately selanazofurin is highly toxic at therapeutic concentrations, making it an unsuitable therapeutic. Compounds such as **168** show in vitro activity against HIV at nanomolar concentrations, below the level at which toxicity is observed.

The 7-azabenzisoselenazol-3(2*H*)-ones (**169**) (Fig. 12), substituted at the 2-position with phenyl or alkyl groups, and the methiodides (**170**) were found in the antiviral assay to be strong inhibitors of cytopathic activity of herpes simplex type 1 virus (HSV-1) and encephalomyocarditis virus (EMCV), more potent than ebselen. The minimal inhibitory concentration (MIC) values were in the range 0.4–6.0 μg mL^{-1}, substantially lower than those when toxicity was observed. The vesicular stomatis virus (VSV) remained resistant toward tested compounds, except moderately active methiodide (**171**) [51, 271].

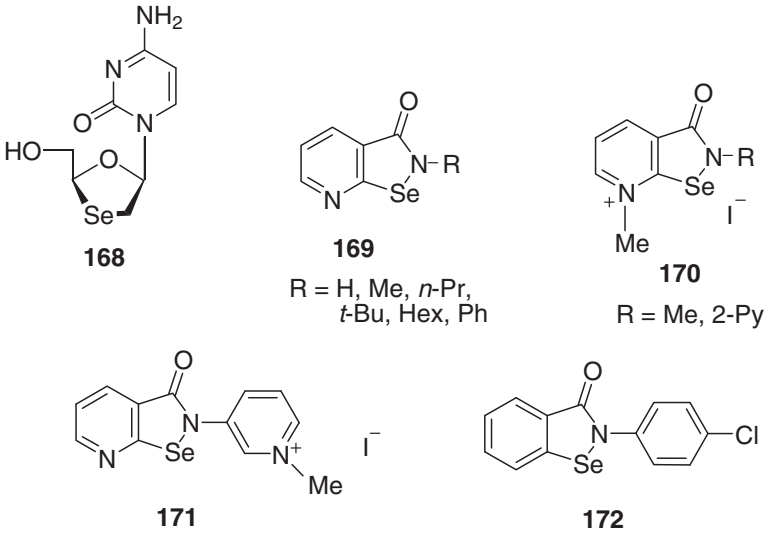


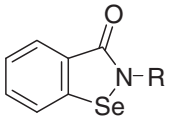
Fig. 12 Antiviral and antimicrobial selenaheterocycles

The antibacterial activities of ebselen and several other benzisoselenazo-3(2*H*)-ones against Gram-positive and Gram-negative bacteria have been reported and it has been postulated that their action is due to the reactivity with essential SH groups [21, 271]. Ebselen as well as the *p*-chloro analog (**172**) exhibited strong inhibitory activity against the growth of fungi *Saccharomyces cerevisiae* and *Candida albicans* strains [272]. Several benzisoselenazo-3(2*H*)-ones were tested in vitro against pathogenic bacteria, yeasts, and filamentous fungi *Aspergillus niger, Penicillum chrysogenum*, and *Penicillum citrinum*. The broadest spectrum of activity was observed for the 2-methyl-7-azabenzisoselenazol-3(2*H*)-one (**169**, R = Me) (MIC = 2.0–32.0 μg mL^{-1}) [259].

The cytokines such as interleukins (ILs), interferons (IFNs) and tumor necrosis factors (TNFs) are the stimulants that play an important role in the mammalian immunological systems. It was revealed that ebselen, several other benzisoselenazo-3(2*H*)-ones, and open-chain bis(2-carbamoyl)phenyl diselenides induce cytokines IL-2, IL-6, TNF-a, and IFN-g in human blood leucocytes. Among the benzisoselenazol-3(2*H*)-ones, the highest activity was exhibited by ebselen and the compounds **173** and **174** (Fig. 13) [92, 153, 273]. Several benzisoselenazol-3(2*H*)-ones were also studied for their immunological activities in mice, rat cells, and chickens. These studies suggest that the process of cytokine induction by organoselenium compounds is species-specific. The drugs that were active in the human PBL were found to be inactive in mouse, rat, and bovine cells [274–276].

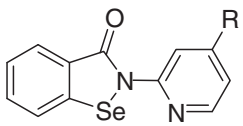
5.3 Electroconducting Materials

Over the past three decades, a number of research groups exploring the field of organic electronics have focused their interest on the potential use of organic semiconducting materials as a low-cost alternative to silicon. Applications for organic semiconductors include organic thin film transistors (OTFTs), light-emitting diodes (OLEDs), photovoltaic cells, sensors, and radio frequency identification (RF-ID) tags for integration into low-cost, large-area electronics. The main advantages of



173

R = H, Me, *t*-Bu, $C_{12}H_{25}$, $C_{18}H_{37}$
CH_2-3-Py, 4-$PrOCOC_6H_4$



174

R = NO_2, Cl

Fig. 13 Selenaheterocyclic immunomodulators

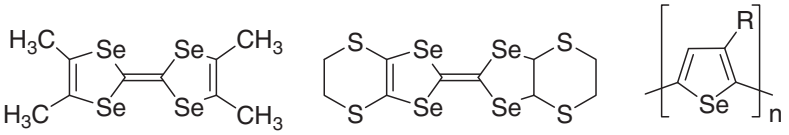
using organic materials lie in cost and processibility. Organic materials that are suitably modified are compatible with solution processing techniques, thereby eliminating the need for the expensive lithography and vacuum deposition steps necessary for silicon-based materials. Low-temperature solution processing also expands the repertoire of tolerant substrates and processing options, allowing flexible plastics or fabric to be used in conjunction with methods such as spin-coating, stamping, or inkjet printing [277].

The most likely prospects have been the compounds having heterocyclic moieties, including selenafulvalenes and π-conjugated polyselenophenes. Some examples are tetramethylselenafulvalene (TMTSF) (**175**), bis(ethylenedithio)tetraselenafulvalene (BETS) (**176**), and poly(3-alkylselenophenes) (**177**) (Fig. 14) [5, 25, 278].

Like their sulfur analogs, tetraselenafulvalenes and the mixed sulfur-selenium systems are excellent electron donors, while being able to form radical cation salts and charge-transfer complexes with appropriate electron acceptors. Interest in the selenafulvalenes culminated in 1980 when superconductivity in an organic metal was discovered for the first time in a salt of tetramethyltetraselenafulvalence $(TMTSF)_2X$, where X = PF_6, AsF_6, SbF_6, TaF_6, ReO_4, FSO_3, ClO_4 [5].

Until the beginning of the 1990s, there was no example of magnetic molecular conductors in which p metal-like conduction electrons and magnetic moments coexisted at low temperature. When using bis(ethylenedithio)tetraselenafulvalene BETS molecules and typical magnetic anions such as $FeCl_4^-$ and $FeBr_4^-$, various types of new magnetic conductors were discovered, including the first antiferromagnetic and metamagnetic organic metals and antiferromagnetic organic superconductors. In addition, conductors exhibiting unprecedented superconductor–insulator transitions, and field-induced organic superconductors have been reported [25].

More recently, a simple one-pot synthetic method for a series of 4,5-alkylenedichalcogeno-substituted 1,3-diselenole-2-selenes, the key precursors of tetraselenafulvalene-type electron donors, was reported. It was based on the treatment of trimethylsilyl acetylene with butyllithium, selenium, carbon diselenide, and finally α,ω-bis(chalcogenocyanato)alkanes. The selenium organoconductors designed for practical application are modified double-bridged selenafulvalenes, the tetraselenafulvalenephanes (**180**). They were obtained from bis(ethynylthio)alkynes (**178**) metallated with butyllithium and then treated consecutively with selenium powder and carbon diselenide to give **179** in moderate yields. The subsequent double-coupling



175 **176** **177**

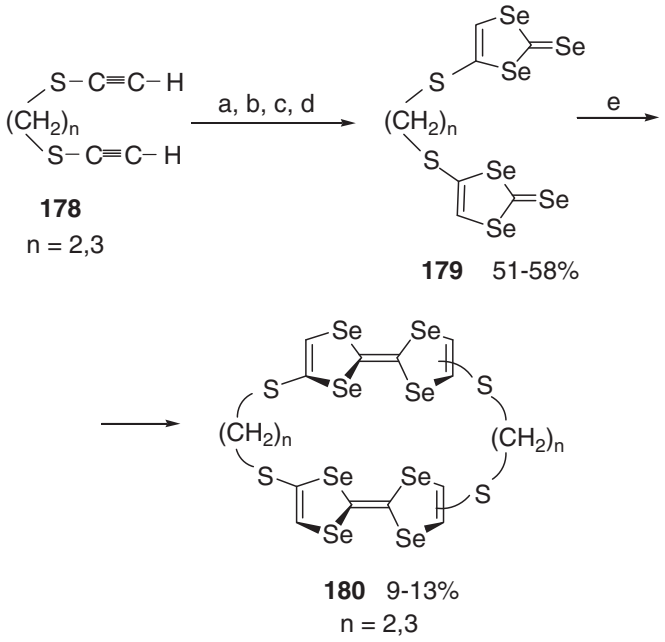
Fig. 14 Selenafulvalenes and polyselenophenes

reaction of **179**, induced by trimethyl phosphate in refluxing toluene, gave the final products (**180**) (Scheme 45). The precise molecular structure of the *cis–trans* isomer was determined by an X-ray crystallographic analysis. It provided evidence that two tetraselenafulvalene units are almost planar and stacked with partial overlap. The conductivity of **180** ClO_4 (n = 2) at room temperature is 3.5 S cm^{-1}, which is one order of magnitude higher than that of its sulfur counterpart [279, 280].

Very recently, a general method for the preparation of alkylenedithio- and bis (alkylenedithio)tetraselenafulvalenes including BETS (**176**) was reported, and a CSe_2-free synthesis of the key intermediate, 2,6(7′)-bis(methylthio)3,7(6′)-bis (2-methoxycarbonylethylethylthio)tetraselenafulvalene, from parent selenafulvalene was presented [281].

π-Conjugated polymers have been the subject of many papers [282]. Many polyheterocycles are constituted of recurring five-membered rings, among them polyselenophenes (PSs) and their derivatives. These have been synthesized and characterized. They result from the polymerization of selenophenes, which may be effected chemically [283–285] or electrochemically [286–288].

The most notable property of these materials is the electrical conductivity, which results from the delocalization of electrons along the polymer backbone. Their optical properties respond to environmental stimuli, with dramatic color shifts in response to changes in solvent, temperature, applied potential, and



Scheme 45 **a** *n*-BuLi, THF, TMEDA, –78 °C; **b** Se (powder), –78 °C then 0 °C; **c** CSe_2, –90 °C then 20 °C; **d** H_2O_2, 20 °C; **e** $P(OMe)_3$, $PhCH_3$, reflux

binding to other molecules. Both color changes and conductivity changes are introduced by the same mechanism – twisting of the polymer backbone, disrupting conjugated polymers attractive as sensors that can provide a range of optical and electronic responses.

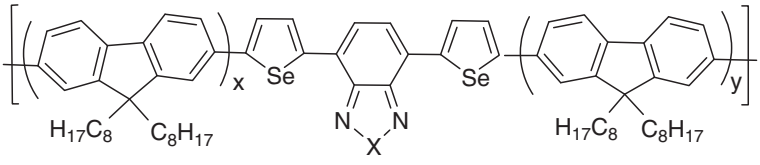
Electrons are delocalized along the conjugated backbones of conducting polymers, usually through overlap of orbitals, resulting in an extended π-system with a filled valence band. By removing electrons from the π-system ("p-doping"), or adding electrons into the π-system ("n-doping"), a bipolaron is formed.

Simultaneous oxidation of the conducting polymer and introduction of counterions dissolved in the solvent can associate with the polymer as it is deposited onto the electrode in its oxidized form. A variety of reagents such as iodine and organic acids have been used to dope PSs.

Since the mid-1980s, more than 60 patents concerning selenophene derivatives have been filed. They generally deal with polyselenophenes that can be used as electroconducting films and photosensitive materials. New long chain alkylselenophenes were synthesized and the effects of the position and of the length of the alkyl chain have been established [1]. Mixed thienyl–selenienyl polymers were prepared and their properties investigated [289]. Poly-2-vinylselenophenes are claimed to have a higher conductivity than their sulfur analogs [290].

A novel electrically conducting polymer containing selenophene and ethenyl spacer, poly-1,2-bis(2-seleninyl)ethene (PDSE), has been generated by chemical and electrochemical polymerization. This polymer exhibits a significantly lower band gap (1.61 eV) than the polyselenophene and possesses partial solubility in common organic solvents [278]. A series of novel copolymers (**181**) (Fig. 15), designed as deep-red electroluminescent materials derived from 9,9-dioctylfluorene and the two Se-containing monomers, were prepared by the palladium-catalyzed Suzuki cross-coupling [291]. Other π-conjugated conducting copolymers contained selenophene rings were also reported [23, 292].

The π-conjugated polyselenophene named PEDOS (**182**) the analog of poly-3,4-ethylenedioxythiophene (PEDOT) [281], one of the most successful conductive polymers, was obtained from 3,4-ethylenedioxyselenophene (**89**) using different polymerization techniques. These were: oxidative chemical polymerization, solid-state polymerization, transition metal-mediated polymerization, and electrochemical polymerization (Scheme 46) [293, 294]. The derivatives of PEDOS having the



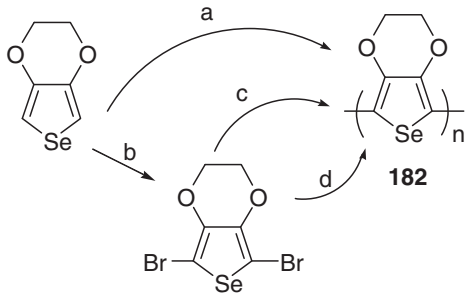
181 X = Se, S

Fig. 15 Selenophene copolymers

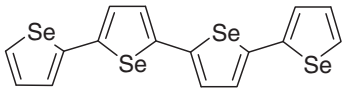
dioxy moiety on 3,4-positions replaced by disulfur, and ethylene by propylene, were also synthesized [293, 295].

Selenophene oligomers are promising compounds applicable to organic field effect transistors, photodiodes, light-emitting diodes and their integrated devices. For this purpose α-quaterselenophene (**183**) and 2,7-diphenyl[1]benzoselenopheno [3,2-*b*] [1]benzoselenophene (**184**) (Fig. 16) were synthesized and characterized [22, 277, 296, 297]. The devices based on **184** exhibited excellent p-channel field-effect properties with hole mobilities >0.1 $cm^2 V^{-1} cm^{-1}$ and current on/off ratios of ~10^6. This high performance was essentially maintained over 3000 continuous scans between Vg = +20 and −100 V and reproduced even after storage under ambient laboratory conditions for at least one year [22].

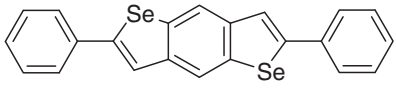
Heterocyclic thiazyl radicals hold considerable potential in the design of both conductive and magnetic materials. In the pursuit of improved conductivity, a series of resonance-stabilized radicals based on diselenadiazoles, sulfaselenazoles, and diselenazoles were obtained (**185**–**188**) (Fig. 17) [298–303]. Structural analyses of **187** and **188** (R^1 = Me, R^2 = H) confirm that lattice and π-delocalization energies are sufficient to prevent solid state dimerization of the radicals. Incorporation of selenium leads to a dramatic increase in conductivity and reduction in thermal activation energy relative to sulfur-based radicals [300].



Scheme 46 **a** $FeCl_3$ or electrochemical polymerization, **b** NBS, **c** $Ni(COD)_2COD$, bipyridine, **d** 50 °C, solid state polymerization

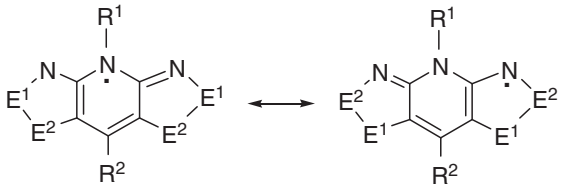


183



184

Fig. 16 Oligoselenophenes



	E^1	E^2
185	S	S
186	S	Se
187	Se	S
188	Se	Se

Fig. 17 Sulfur and/or selenium-containing neutral radical conductors

6 Concluding Remarks

During the last two decades, the chemistry of organoselenium compounds, including those having selenaaromatic rings and their nonaromatic congeners, received a new impetus. It resulted in a broad spectrum of their possible use as reagents and catalysts, pharmaceuticals, and new materials for electronics. Interest in the use of organoselenium compounds in biochemistry started with the findings that they are much less toxic than the inorganic selenium species. The low-volatile organoselenium compounds, including selenaaromatic compounds, may be employed as reagents or catalysts in synthetic practice without special precautions, although direct contact with skin should be avoided.

More recently, scientific effort has been concentrated mainly on the most common groups of selenaaromatic compounds, such as selenophenes, 1,2-selenazoles, 1,3-selenazoles, selenadiazoles, seleninium salts, on the new selenium-containing macrocycles, the selenaporphyrins and their analogs, and on the selenaheterocycles having a nonconjugated heterocyclic ring, the benzisoselenazol-3(2*H*)-ones and resonance stabilized radicals based on diselenazoles, diselenadiazoles, and sulfaselenazoles. Although most of the methods for their preparation are traditional, some substantial improvements in the ring synthesis have been obtained. Modification of the parent structures by introduction or replacement of the substituents is an alternative way of obtaining compounds designed for their practical use.

The aromatic selenaheterocycles such as selenophene (**1**), 1,3-selenazole (**3**), 1,2,5,-selenadiazole (**5**), 1,2,4-selenadiazole, and 2,1,3-benzoselenadiazole undergo [1,4]cycloaddition followed by spontaneous deselenation, which is convenient way for construction of alkynes and selenium-free heterocycles. Benzisoselenazol-3(2*H*)-ones, particularly ebselen (**59**, R = Ph), are efficient oxygen-transfer catalysts for hydroperoxide oxidation of various groups of organic compounds and most of these reactions have a synthetic value because of their selectivity and high product yields.

The unique redox properties and ability to react with the cellular nucleophiles are influential in the catalytic and biological activities of organoselenium compounds, including those where selenium is a part of the heterocyclic ring. Selenazines,

1,3-selenazoles, cyclic seleninate esters, spirodioxyselenuranes, and cyclic selenenamides, particularly benzisoselenazol-3(2*H*)-ones, possess therapeutic potential against various diseases as antioxidants, enzyme inhibitors, antiinflammatory and anti-infective agents, and immunomodulators.

Various types of new conductors having a selenaheterocyclic ring system have been obtained and characterized. π-Conjugate tetraselenafulvalenes and the mixed sulfur-selenium systems form radical cation salts and charge-transfer complexes with appropriate electron acceptors. The bis(ethylenedithio)selenafulvalene is an example. Using its salts with typical magnetic anions, new magnetic conductors exhibiting unprecedented superconductor–insulator transitions and field-induced organic conductors were obtained. Resonance-stabilized radicals based on diselenadiazoles, sulfaselenazoles, and diselenazoles are both conductive and magnetic materials, and new electrically conducting polymers containing selenophene have been obtained and characterized. The selenophene oligomers are prospective compounds applicable to organic field effect transistors, photodiodes, light-emitting diodes and their integrated devices.

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