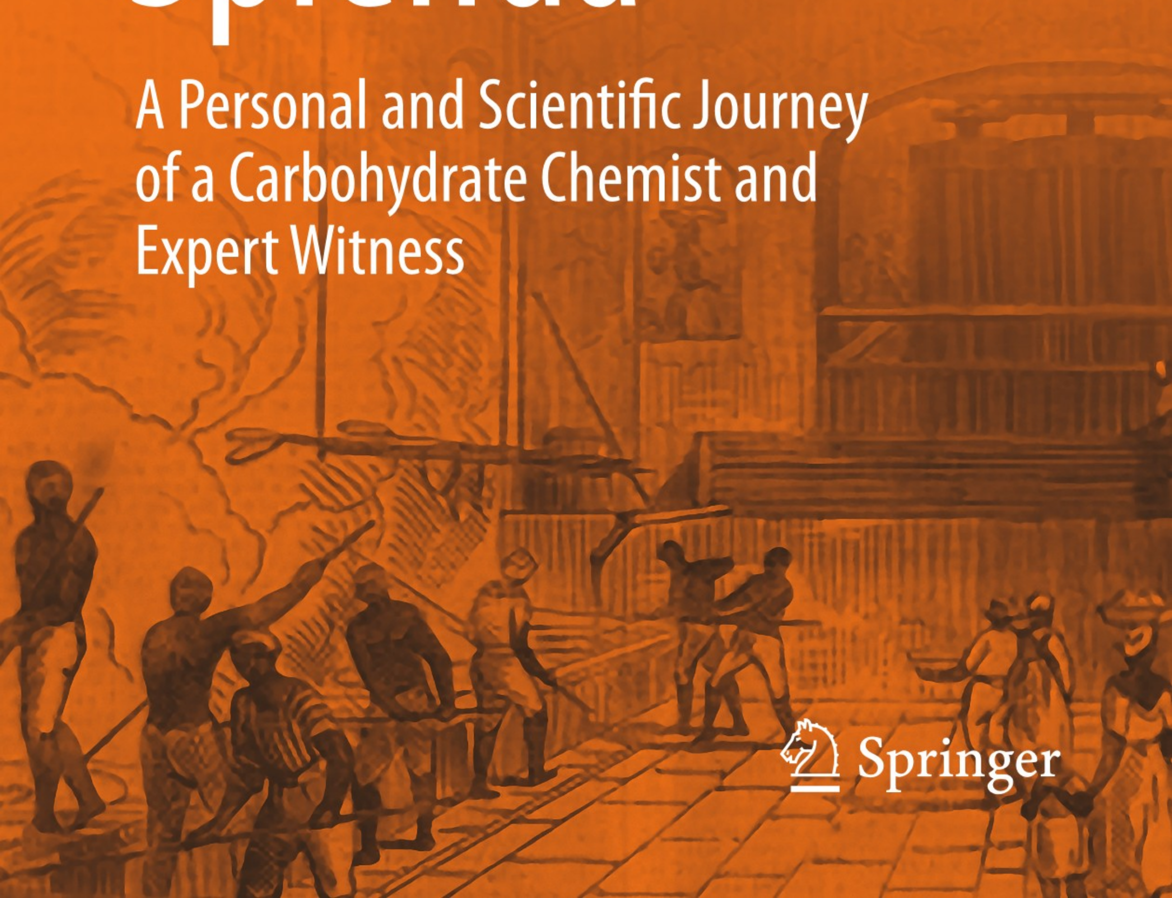
Bert Fraser-Reid

From Sugar to Splenda

A Personal and Scientific Journey of a Carbohydrate Chemist and Expert Witness



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Cover image: The Interior of a Sugar Boiling House (1840) from the London Illustrated News, June 9, 1840. (Courtesy of the National Library of Jamaica).

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Dedication

I dedicate this book to the two women who, in different ways, have made it possible.

Joyce, the surviving of five siblings, has been a surrogate mother, ever since our real mother died when I was 9 months old, and she a preteen of 12 years. She continues to bless me with love and her never—failing concern about my health and well-being. Thanks to her, I cannot lament that I did not know my mother, nor a mother's love.

Lillian, my wife of 48 years, has "brought me up" along with daughter, Andrea, and son Terry. Sometimes I think she had an easier time with them. She has been a sounding-board for my bright ideas – such as writing this book. Her patience, love and support have been severely stretched during the last three years – but still they remain unbroken. The blessing of our true family begins with her, and envelopes our wonderful children and grand children.

Pittsboro, NC, USA
Bertram Fraser-Reid

Preface

The patent infringement litigation that is summarized in Chapters 7 – 17, is the impetus that prompted me to write this book. Actually, the impetus was multifaceted; but all facets converged to bring about my presence as an expert witness, in the Court of the United States International Trade Commission.

As a native Jamaican, the history, ramifications, politics, manufacture, economics etc. of "sugar" were absorbed subliminally, and this was apparent as I approached Chapter 1. But it was at Canada's Queen's University that I realized, among other things, that sugar was actually not singular, but plural. And it was there that, by pure chance in 1958, I happened to be around, when the early experiments that led "from Sugar to Splenda" were underway. These biographical issues are abstracted in Chapters 2 and 3, including my unlikely journey from a Jamaican High School, where neither chemistry nor physics was taught, to being an expert witness about chemistry in a trial with huge international and commercial consequences.

The middle of the book, chapters 4 – 7, contains the "meat and potatoes", because the allegedly infringed patents were all about chemistry – 100%. However, that percentage was diminished markedly at the hands of brilliant lawyers who refused to accept the teaching of brilliant chemists.

I have therefore tried to give the readers a user-friendly presentation of the chemistry at issue in Chapter 4. Those wishing less user-friendly treatments of the chemistry should see Appendices A, B, C, D and E.

2200 pages of the Public Court Transcript of the trial have been whittled down to Chapters 8 – 17.

Introduction

I learned that Tate & Lyle had lost the patent infringement claim on September 22nd 2008 via an e-mail from attorney Gary Hnath, who was then with the Washington law firm Bingham McCutchen. At the time I was on vacation with my wife and sister on the picturesque extremities of Canada's Gaspé Peninsula. I had been an expert witness for one of the Respondents in the litigation, had enjoyed the experience, and had found it immensely educational – and not only about the law.

The patent infringement was concerned with the artificial sweetener SPLENDA. The sweet agent in this sweetener is called sucralose – not to be confused with sucrose. In fact it is 600 times sweeter than sucrose (table sugar) from which it is manufactured by controlled chlorination. Because of its intense sweetness, sucralose is present to only 1% in SPLENDA, the other 99% being a neutral "filler". Unlike sucrose (table sugar), sucralose is not broken down in the body. It is therefore non-caloric, cannot produce energy, and most importantly cannot be stored as fat. It is also unaffected by moderate heating and hence, unlike most artificial sweeteners, can be used in cooking; and unlike others, it has no aftertaste.

These properties have given SPLENDA a favoured status among high-intensity sweeteners, encouraging the advertisement that SPLENDA is "made from sugar, so it tastes like sugar", to which manufacturers of another artificial sweetener, Equal, took exception. The resulting trial was discussed, in an article entitled *Legally Sweet* by chemistry Nobel Laureate Roald Hoffmann in *American Scientist* volume 95, 2007. An Editor's note about the article states that the "trial ended in a settlement (terms not disclosed)------."

My involvement with the patent infringement case began with the arrival of an e-mail on April 30, 2007. Ed Pardon, a lawyer from Madison, Wisconsin, was interested in engaging my services. I had been recommended to him by William Roush. Bill, a generation younger than me, is an eminent organic chemist whom I have known since his days as a Harvard Ph.D. student studying with R.B. Woodward, the most celebrated organic chemist of our age. Bill is now executive director of Medicinal Chemistry at Scripps Institute (Florida), and also is an associate editor of the *Journal of the American Chemical Society*. Clearly both duties do not leave time for being an expert witness.

Mr. Pardon informed me that Tate & Lyle, arguably the world's leading sugar entrepreneur, had brought a lawsuit against four Chinese manufacturers for infringing its sucralose patent, and also against several Chinese and US distributors, for trafficking in Chinese-made sucralose. Since there were trade issues involved, the United States International Trade Commission (ITC) also had an interest. Accordingly, there would be a trial at the Commission's headquarters in Washington, D.C.

It was in connection with the ITC that I was engaged by Mr. Gary Hnath, Esq. He explained that "my" Chinese Respondent was Guangdong Food Industry Institute (GDFII) which is located in Guangzhuo in Southern China, approximately 100 km from Hong Kong. The city, with a population of 20,000,000, was previously known as Canton. Actually my wife and I had visited Guanghzhuo in 1991 when I was on a lecture tour of China. I had given a lecture at the Sun Yat-Sen (now Zhongshen) University, located in this historic city.

I had been somewhat familiar with Sun Yat-Sen's fascinating history. But of greater interest to me was the fact that most of the Chinese who were brought to Jamaica by the British as indentured laborers after the abolition of the West Africa Slave Trade (see Sect. 1.2), had hailed from Canton. There are now many descendants of that initial group in Jamaica. Indeed, one of the island's most popular band leaders, the late Byron Lee, comes to mind.

I was required to visit the GDFII factory in order to gain a firsthand knowledge of the manufacturing process. My visit was timed to coincide with a tour of the plant by representatives from the firm of Finnegan, Henderson, Farabow, Garrett, & Dunner (hereafter "Finnegan Henderson") which represented the Complainants, Tate & Lyle.

Much more will be said about this dual purpose visit in Sect. 7.8, but at this point, I can report that I came away convinced that no infringement of Tate & Lyle's patents was taking place.

My finding was in no way influenced by the elegant dinner hosted by the GDFII board of directors for Mr. Hnath and me. Conversation moved very smoothly around the dinner table thanks to an energetic lady, Ms. Dion Shao, who apart from being a translator, handled just about all organizational aspects of our visit. She was the head of Human Resources Department of GDFII in spite of only being in her mid-20s.

I was asked to say something about my impressions of the visit. Apart from telling them that this was my second visit to their city, I mentioned that I had been involved in the sucralose story for nearly 50 years. There was much fussing and humming with widened eyes staring at me. Dion explained that they wanted to know my age, because they thought that I was about 55 years old, and therefore couldn't understand how I could have been "involved" with sucralose for 50 years. I told them that I was 73. That also caused much huffing and humming and widened eyes staring at me. I, through Dion, explained that I got good genes from my father, and if they could see my 86 year old sister, they would understand.

My "involvement" with sucralose was fortuitous in many respects. To begin with, that I am a chemist of any sort, results from the confluence of much luck – good and bad. I was a school-teacher three years out of high school in my native Jamaica when I made my first contact with chemistry in 1955. I had resolved to pursue the subject as a career after reading the 235 page self-help book *Teach Yourself Chemistry*. It was my further good luck in 1956, that when I applied to various Canadian universities, Toronto and McGill, where I had friends, had finished enrolling new students. Fortunately, Queen's University, mid-way between Toronto and McGill, was still open.

Queen's had recently hired the eminent carbohydrate chemist, J. K. N. Jones (JK) from England's Bristol University to fill the position of Chown Research Professor of Science. I was fortunate to spend an internship in his lab for the summer preceding my final year. This experience, although somewhat catastrophic because of my pathetic laboratory skills, determined how my future was to unfold – including my involvement in this patent infringement case.

My duties as an expert witness caused me to trace the relevant chemistry literature about the history of sucralose. To my great surprise, the search led me back to Queen's University, and to the stunning revelation, that the experiments to install chlorine atoms in sucrose, were being carried out in the Jones laboratory during my undergraduate internship in that very summer of 1958. My ignorance of this historical connection is not because I was unobservant, but because there were so many bewildering activities going on around me. Importantly, Professor Jones had no foresight that a "high intensity sweetener" would evolve from these early experiments. Indeed he was trying to make a pesticide!

A year later, I was admitted to Professor Jones' research group as a graduate student. Joining at the same time were my Queen's undergraduate classmate, Canadian Sol Gunner, and Harry Jennings, a cockney Londoner. After completing our M.Sc. degrees, Sol went to the University of London for his Ph.D., while I went to the University of Alberta for mine.

Jennings remained at Queen's for his Ph.D. and in a string of publications between 1962 and 1966, laid out the mechanism by which chlorine replaced hydroxyl groups in many sugars. With his Ph.D. in hand, Jennings then returned to England for advanced study in the laboratory of Professor Leslie Hough, at Queen Elizabeth (later King's) College, University of London where, within a decade, the sweetness of chlorinated sugars was discovered.

Sucrose (table sugar) is a comparatively delicate sugar. It is sensitive to acids as mild as that present in vinegar, and it decomposes upon mild heating. Its laboratory preparation, once regarded as the Mount Everest of synthetic organic chemistry, was first achieved by Professor Raymond Lemieux, and this was partly responsible for my decision to leave Queen's after my M. Sc., and pursue my Ph.D. under his guidance at the University of Alberta. Notably, the second laboratory synthesis of sucrose was carried out in my lab in 1978 when I was at Canada's University of Waterloo.

Sucrose contains eight hydroxyl (OH) groups. Three of these must be replaced by chlorines in the preparation of sucralose, one of them being particularly difficult to implement. The successful procedure must therefore be, not only highly selective in installing the required three chlorines, but also be energetic enough to address the unresponsive one, while not destroying the rest of the molecule.

Tate & Lyle had invested heavily to be successful in these objectives, and was understandably jealous of its patents.

The three chlorines inserted into sucrose serve to classify sucralose as an organochloride, i.e. an organic compound with chlorine(s) bonded directly to carbon. Similar bonds are found in DDT, and the fame (or infamy) of this compound, which was widely used as a pesticide for over 100 years, has engulfed all organochlorides, past, present and future undoubtedly, including sucralose – and hence SPLENDA.

But why was Professor Jones interested in putting chlorines into sucrose? The good professor passed away in 1977. Fortunately, Dr. Malcolm Perry, Jones' then second-in-command, has been helpful; however the rational analysis that appears in Chap. 6 is the author's own speculation. Thus, Jones *probably* reasoned that partially chlorinated sugars, would contain carbon-chlorine bonds like DDT, and hence would "hopefully" be pesticides. But unlike DDT, the partially chlorinated sugars would dissolve in water where they would suffer bio-degradation.

Professor Jones' impetus to insert chlorines into sugar, may therefore have been driven by rational scientific curiosity; but it was also timely, for such an out-of-the-box fantasy was opportune in the 1950s. There was a burgeoning surplus of sucrose on the world market, arising from sugar beets grown in the temperate zones of Europe and USA. Funding to do research, to get rid of the excess sucrose was readily available.

Hough and his colleagues in England also enjoyed such "readily available" funding; but their interest was in "modified sugars", particularly where chlorine or nitrogen replaced hydroxyl (OH) groups. Such modifications were seen as intermediates *en route* to antibiotics – not to pesticides. Jennings work in Jones' lab on chlorinating sugars was therefore relevant. However, that a "high intensity sweetener" lay in waiting was as foreign to Hough as it was to Jones.

In light of the organo-chloride content, there was understandable concern about using sucralose as an artificial sweetener. As far as the author is concerned, these fears have been dispelled, and some comments about the "safety" issue are made in Sect. 5.2, and some popular prescription drugs that fall into this category are noted.

Independent tests have shown that sucralose is neither carcinogenic nor toxic. Nevertheless, admission to United States markets was forbidden for a long time. By contrast, the Canadian Food and Drug Directorate gave its approval a decade earlier, and so markets in Canada were open to SPLENDA in 1991.

By further remarkable coincidence, the Officer of Canada's Food and Drug Directorate in Ottawa, who gave the approval to SPLENDA was Dr. Solomon Gunner. Sol was my 1959 undergraduate classmate at Queen's University - and we were M.Sc. lab mates of Jennings in Jones' lab 1959–1961. The three of us, in our third floor perch, were unwittingly destined to become connected, somehow, to the sucralose story that begun with the chlorination of sucrose on the floor beneath us.

This subliminal connection of sucralose to my own history, to Professor J. K. N. Jones my M.Sc. mentor, to Drs. Harry Jennings and Sol Gunner, my graduate school classmates, and to Professor Leslie Hough and Dr. Riaz Khan my professional peers, is one of the narratives of this book.

The recurrence of this artificial sweetener at various stages of my career is of further interest because my father was a type 2 diabetic, and he indulged my childhood curiosity by allowing me to taste the little white pill, which was his "sugar." He told me it was called saccharin. Two of my five siblings and I are/were type 2 diabetics. I prefer saccharin (Sweet and Low in the red packet in the US), my diabetic sister prefers cyclamates (Sugar Twin in the yellow package in Canada), while my weight-conscious relatives stick to SPLENDA upon my strong recommendation.

Although I have had the pleasure of discussing the history of sucralose with Professor Hough and his former student and co-inventor Dr. Riaz Khan, I have reconstructed the chronology, the thinking, and the *raison d'etre* behind the evolving science, by relying entirely on Parts I to Part XXI of the series of publications from the Hough group entitled "Sucrochemistry". This is necessary because as noted above, the pursuit of an artificial sweetener was not the initial objective of the research programs of either Jones or Hough.

Similarly, I have relied on the issued patents to disclose developments in the manufacturing process, after the project had moved from Hough's lab at the University of London, to Tate & Lyle's laboratories.

Another narrative in this book concerns the intersection of law and chemistry. These roles were not always congruent. Since the issues would not be resolved by experiments in my chemistry laboratory, I soon learned to appreciate the "big picture" in the court of law.

And this is as it should be. If the litigation rested on "hard" carbohydrate chemistry, the trial would have lasted 2 h, maximum, instead of eight days. Issues such as whether documents were presented by specified dates, or whether qualified experts would be recognized as experts, or whether an expert could be a witness for both sides of the litigation, etc. were much more entertaining than "hard" chemistry. Indeed as far as the author was concerned, many of the lawyerly effusions were sometimes overstated issues of semantics, which only added to the unfolding drama.

"Well, it may be semantics, but it is important to this case" was the outburst from one of the trial lawyers for Tate & Lyle.

The slave ancestors of this Jamaican author undoubtedly helped to produce the unrefined sugar that was sent to England to be refined by, and enrich the Tates and the Lyles independently, before the families merged their fortunes. For this descendant of slaves to appear as an expert witness for the Respondents in a patent infringement case in which Tate & Lyle is the Complainant is a very strange twist of fate.

Acknowledgement

First, I thank Dr. William Roush for recommending me as an expert witness to attorney Ed Pardon, who then recommended me to Gary Hnath, Esq. By accepting Bill's recommendation, Gary unwittingly initiated the search that led me to the uncanny realization that I had been a summer intern in the Chemistry Department of Queen's University, Canada, in 1958, when chlorination of sugars was being explored in the lab of the late Professor J. K. N. Jones. After the trial was over, and the idea of this book materialized, Gary continued to show interest, and I thank him for his occasional advice, without billing me at a law-partner's hourly rate.

Professor Jones became my M. Sc. supervisor one year after my internship. Dr. Malcolm Perry, then Jones' second-in-command, enthusiastically shared his recollections of the 'whys and what-fors' behind Jones' 1958 chlorination adventures with sugars. My M.Sc. classmates in Jones' lab, Drs. Sol Gunner and Harry Jennings, also have connections to the SPLENDA epic, as we detail in these pages.

I thank Professor Leslie Hough, (Jones' first Ph. D. student) and Dr. Riaz Khan (a Hough student., who subsequently became Tate & Lyle scientist) for enthusiastic exchanges of information, and for reading Chapter 4 in its entirety, to ensure that their work was accurately reported. Hough's then post-doctoral fellow, Dr. Shashikant Pfadnis, provided a recollection of his legendary Eureka moment, when he discovered that chlorinated sugars are sweet.

I am grateful to Dr. Earle Roberts of Jamaica's Sugar Research Institute and His Excellency Mr. Anthony Johnson, Jamaica's Ambassador to London, for helping to me delve into Jamaica's storied sugar history. Jamaica's National Library was most accommodating during my visits to the Library and to my sometimes abstruse requests; but in the end, the Library produced treasured historical material, some of which is on the outside and the inside this book.

My colleagues friends Drs. Cristóbal López and Ana Gómez took over the task of "uploading" the manuscript – the original as well as the proof, from their labs in

Madrid, Spain, thereby sparing me from taxing my rudimentary computer skills. Drs. Siddhartha Ray Chaudhuri and Srinivas Battina combined their computer and photographic expertise to prepare or modify all the photographs in the book.

Springer personnel have been very accommodating to my diffuse requests, and special thanks go to Ms. Elizabeth Hawkins for her patience

Contents

Chapter 1
Jamaica

1.1 An Unforgettable Introduction to 'Suga' Manufacturing

My contact with the manufacture of sugar began at the early age of 6 or 7. It was memorable. We lived at Bryce, a village high in the central mountains of Jamaica, where my father was the principal of the local elementary school. He was addressed as "Teacher", even by the school's other teachers! About 200 yards from our house, the "Teacher's Cottage", was Mr. Thyme's "suga' mill". Located in a clearing about half-an-acre in size, there was just enough space to accommodate the single grinder, the teeth of which could squeeze the last drop of juice from a stalk of cane so efficiently that you could light it with a match – or so it seemed. The mill was powered by a single dutiful donkey that treaded lazily along a well-worn circular path.

Local farmers would arrive with their donkeys laden down with long stalks of sugar cane. These had to be cut into two-foot lengths to be fed into the teeth of the grinder. This cutting was done manually by means of a sharp machete. I remember how sharp this instrument had to be, because one day I decided to help with the cutting. The middle finger of my left hand got in the way of the razor-sharp machete, and in the resulting commotion I fortunately had the good luck, for it wasn't common sense, to hold the dangling tip in place with my thumb while I ran home. Pixie, my sister, older by one year, panicked and preceded me home, yelling that "Bertram chop off 'im han'." Fortunately, my grandmother had a more realistic perspective. She bandaged the dangling piece securely, and the offended third finger was soon as good as new, and I was back to playing the piano, dispelling my greatest fears.

So began my earliest participation in the manufacture of sugar. It was more than six decades before I would play an active part again – this time as an expert witness in an alleged patent infringement case before the United States International Trade Commission (ITC) in Washington DC.

B. Fraser-Reid, *From Sugar to Splenda*,
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I will tell about my improbable journey from Mr. Thyme's sugar mill to the United States International Trade Commission, reliving some of the strange circumstances that lay between Jamaica and Washington.

But first an even briefer summary of Jamaica and sugar.

1.2 A (Brief) History of Sugar and Jamaica

1.2.1 Sugar and Jamaica Were Once Synonymous

In *Bury the Chains,* Adam Hochschilds captures the wealth and riches of the Jamaican sugar industry with this *vignette.* "King George III once encountered an absentee owner of a Jamaican plantation whose coach and liveried outriders were even more resplendent than his own. 'Sugar, sugar, eh?' the King exclaimed. 'All *that* sugar!' " [1].

In 1773 "British imports from Jamaica was five times that from the thirteen mainland colonies" of the nascent United States, and imports from the tiny Caribbean island of Grenada was eight times more than all of Canada" [1, p. 54]. An unattributed source reports that during negotiations after one of the never-ending stack of wars, the British negotiator offered a choice between Canada and Jamaica. Not surprisingly, his opposite ridiculed the idea that "one would choose some fur hats over a luxury like sugar". Evidently the British negotiator must have decided to keep both the fur hats and sugar, because Canada and Jamaica remained members of the British Commonwealth.

The *white*, granulated sugar which may be purchased at any corner store, is the world's largest mass produced, absolutely pure chemical. An index of purity that is used commonly by chemists, is the sharpness of the melting point of a crystalline substance. When crystals of *organic* compounds like sugar are subjected to slowly increasing heat they suddenly melt, and become gooey. This melting point is a criterion of purity, and range of 1–2°C is excellent. This standard is met by store-bought *white* sugar.

The *brown*, granulated version, still tainted with a bit of molasses, may not melt as sharply; but some people find it more tasty.

(Salt, being an *inorganic* substance, does not have a melting point. If heated high enough such substances just disintegrate and spatter).

Historically, tropical and subtropical regions of the globe, such as Brazil, the West Indies, India, Fiji, the Southern USA and Northern Australia, provided sugar from sugar cane. Today, sugar beets are the source of sugar in the temperate zones of Europe and Northern USA. This sugar cane *versus* sugar beets demographic, presents a historical mirror to European colonialism.

There is scholarly debate about the origin of the "granular material" that according to Peter Macinnis in *Bittersweet*, existed "all over the world", notably in Persia as early as AD 263 [2]. However, there is general agreement that the origin of sugar, as a commodity, dates back to India in A.D. 350. By the end of the first millennium, Europe had embraced this delicacy that was an excellent substrate for crafting elaborate, artistic confections. Westminster Abbey was decorated with “fighting knights and dancing ladies” made from hardened sugar. Mintz reports that “Communion wafers were commonly baked in the shape of testicles” [3].

Not surprisingly, it was not long before sugar had displaced honey as a source of sweetness. This development was viewed with dismay by many, including the eminent scientist/philosopher Francis Bacon, who advocated the health benefits of honey.

However, transportation of the commodity from India was costly and risky since the pathway, if overland, traversed hostile nations of the Ottoman Empire and, if by sea, had to negotiate the treacherous waters of the Cape of Good Hope.

By 1400, Portugal’s maritime excursions had probed the western coastline of Africa, leading down to the island of *São Tomé* off the coast of today’s Gabon. They started to cultivate sugar cane, and to cope with the demands of this activity, slaves were engaged. According to Elizabeth Abbott in *Sugar*, among the first unfortunates to be so demeaned, were “two thousand Jewish children, aged two to ten—Their parents had recently fled to Portugal from Spain, where the Inquisition was forcing Jews to convert to Roman Catholicism” [3, p. 19]. But as “sugar became a bigger and bigger player in the world’s politics”, greater efficiency was required, and so the Portuguese “soon afterwards brought in black slaves” from the African mainland to *São Tomé*.

This reprehensible strategy for sugar cane cultivation was soon to expand geometrically. Elizabeth Abbott in *Sugar* reports that in his second (1493) voyage to his recently “discovered” lands, Columbus’ cargo included sugarcane from the Canary islands along with a surreal directive—signed by King Ferdinand and Juana ‘the Mad’. This directive informed “the indigenous Taino people that the late pope gave these islands—to the above mentioned King and Queen” [3, p. 23] and went on to warn of terrible consequences. The Tainos probably had no concept of who the pope was, but nevertheless, the directive added that should the Taino dispute the pope’s authority “we shall enslave your persons, wives and sons, sell you or dispose of you as the King sees fit—and harm you as much as we can as disobedient and resisting vassals?” [3, p. 23].

The Taino, a delicate people, were ravaged, not only by the brutal labor conditions, but by the diseases that the Europeans brought with them.

Jamaica’s indigenous occupants were Arawak Indians and they suffered similar depredations. But according to Abbot, they were “peaceable” and suffered at the hands of fierce Carib warriors “who inhabited the islands now known as Trinidad, Guadeloupe, Martinique and Dominica”. The Caribs were cannibals with a legendary flesh-lust, and “one warrior claimed that French ‘meat’ was tender but Spanish ‘meat’ was tough, while another boasted that he preferred Arawaks to Europeans, who gave him a bellyache” [3, p. 32]. For one reason or the other, Jamaica’s first-nation population perished.

Other lands “discovered” by Columbus fared similarly. The Portuguese claimed Brazil, the Dutch claimed Surinam. The British, Spanish, and French exchanged the islands of the West Indies archipelago as the spoils of their never ending wars.

The production of sugar in the newly acquired colonial territories required generous, unlimited supplies of inexpensive labor. This need was met by the 300 year history of the West African slave trade, and was essential for the production of sugar in the British West Indies. Unlike plantations in the Southern USA, where slaves were regarded as valuable "property" to be nurtured and bred, the British could rely on their West African colonies to be bottomless sources of new slave labor.

Accordingly, in *Bury the chains*, Adam Hochchilds reports that "[c]aribbean slavery was, by every measure, far more deadly than slavery in the American South" [1, p. 65]. John Newton, then a notorious trafficker in West African slaves advised "little relaxation, hard fare, and hard usage, to wear them out before they became useless, and unable to do service; and then to buy new ones, to fill their places" [1, p. 67]. His advice was clearly followed, as is evident from the fact "when slavery ended in the United States, some 400,000 slaves imported over the centuries had grown to four million". By contrast in the British West Indies, of the two **million** slaves who had been imported, only about 670,000 survived. Clearly then, in the grand history of sugar, the Caribbean must be seen as a slaughterhouse of indigenous West Africans.

How ironic that the same John Newton, the villainous trafficker in slaves should, like Saul on his way to Damascus, "see the light", enshrine his climacteric conversion with the penitent hymn *Amazing Grace* and, then of all things, become a paladin for ending the West African Slave Trade. This endeavor had found resistance in the British Houses of Parliament, because many "absentee owners" of West Indian sugar estates occupied its seats. Notable among their number was the righteous Church of England, which owned the fabulously productive Codrington Estate of Barbados. Christian charity did not prevent the estate's brand from being "burned onto the chests of slaves with a red hot iron" [1, p. 67].

The church's pernicious missionary outreach was apparently being frustrated by the Estate's high death rate, which prompted the plaintive Archbishop of Canterbury to complain: "I have long wondered & lamented....that the Negroes in our plantations decrease, & new Supplies become necessary continually. Surely this proceeds from some Defect, both of Humanity, & even of good policy. But we must take things as they are at present" [1, p. 68]. With such guile in high places, it comes as no surprise that the abolitionists William Wilberforce and Thomas Clarkson encountered decades of resistance in the British Houses of Parliament before the West African slave trade was abolished.

Interestingly, Codrington College of Barbados is today the site of the oldest theological college in the western hemisphere, and it is, of course, still affiliated with the Church of England.

The labor shortages, consequent upon the abolition of the slave trade, were handled adroitly by the British, by changing from trafficking in slaves, to trafficking in indentured laborers from India, Ireland and China. These cross-currents gave rise descendant populations with rich interracial, diverse, texture. This feature is acknowledged in Jamaica's motto "out of many, one people."

West Indies sugar estates remained profitable for hundreds of years, even though production facilities and consumers were separated by thousands of miles across the Atlantic Ocean, perilous to traverse because of storms, hurricanes, pirates and hostile war-mongering neighboring nations.

The climate and soil of the tropics allowed excellent production; but the hilly terrain of the volcanic islands of the West Indies archipelago was not compatible with mechanization. With the abolition of slavery, which followed some 50 years after the end of the trans-Atlantic West African slave trade, mechanization became attractive, driven strongly by the coincidental growth of the Industrial Revolution.

A ready alternative to sugar cane was sugar beets which were identified as a source of sugar only in the 1700s. Cultivation and harvesting of beets are much less demanding, as is the subsequent extraction of the sugar. Competition therefore became more and more unfavorable for the labor-intensive West Indies sugar cane production, and emphasis shifted to territories with more convenient terrain, notably Brazil and the tropical Queensland Province in Northern Australia. Smooth mechanization has made those territories today's major producers of sugar from sugar cane.

European colonial powers, whose prosperity owed so much to West Indian sugar cane production for 300 years, now shifted their source to domestic sugar beets. In 2005, France was the leading producer of sugar derived from beets.

However, there have been several agreements, conferences, conventions and the like, aimed at preserving access to the European Community by former European colonies in the Caribbean and Asia. But not surprisingly, this munificence has not proved sustainable.

But the shift to more easily cultivated beets had a downside. Easy production in the temperature zone caused worldwide production to outpace consumption. The burgeoning excess of sugar, therefore encouraged the development of new uses for the commodity.

One new product of meretricious interest is Olestra, a fat substitute that can be used in cooking. This fatty substance is obtained by coupling sucrose (table sugar) with fatty acids, such as those found in canola and olive oils. Unlike sucrose, olestra is not broken down in the body, and hence it is non-caloric. A decline in blood cholesterol was also touted as an added attribute. As a result, some success was enjoyed in the production of potato chips, tortillas and crackers and such fast-foods that could be made with Olestra instead or ordinary fats. However, the product suffered because of reports that it affected the bowels unpleasantly, causing a dilemma known by the graphic proctologic euphemism "anal leakage".

1.2.2 "Head Sugar": At Least 500 Years Old, And Still Going

Mr. Thyme's sugar mill where my middle finger and a machete had a close encounter was essentially a neighborhood cottage industry to provide head sugar to the village.

The juice from the crushed sugar cane was funneled into a container beneath the crusher, before being transferred to huge cast iron bowl, under which a raging fire was maintained. After bubbling, steaming and frothing for hours, the juice became a dark brown goo. This was then ladled into small tin cups, and set to solidify. The resulting "head sugar" was a mass of imperceptible brown crystals of sugar held firmly together by residual molasses.

In the Jamaica of my childhood, a popular, refreshing drink, commonly known as "wash", was made by shaving the compact, solid product, and dissolving in water. "Wash" was therefore almost reconstituted cane juice, and was commonly drunk by laborers for instant energy. It was also a favorite of little children who, although rarely needing more energy, drank it anyway. The variety, with an added accent of ginger, was to die for.

"Head sugar" was the sweetening agent of the poor and humble, and it contained all the nutrients present in cane juice, albeit modified by the boiling process. The not-so-poor and humble, upgraded themselves to granulated brown sugar, produced by the island's sugar factories, and considered unrefined. This brown unrefined sugar was sent to Britain where it was processed to become the expensive white stuff. The refining process, probably consisted essentially of dissolving the brown sugar in water, decolorizing the solution with charcoal, a common laboratory technique, and concentrating the clear liquid, then setting it to crystallize.

The resulting white crystals were then sent back to Jamaica and, I presume, the rest of the British Commonwealth, upon which the sun never set – in those days. Not surprisingly, this shipping back and forth across the Atlantic, plus the label on the package of the British refiner, usually Tate & Lyle, inflated the cost. So, in the humble homes of Jamaica's rank-and-file, white sugar was served only to impress *hoi poloi* visitors. Upper class pretenders and expatriate notables sweetened their tea with exotic sugar cubes.

How interesting, that today brown sugar, which is championed by health mavens, is more expensive than white sugar, and "head sugar" is even more expensive yet.

I was interested to know if the "Head Sugar" of my youth, was still made in Jamaica seventy years later. From my many visits to India, plus discussions with dozens of young Indian scientists who have spent time in my labs, I knew that Indian cuisine uses a lot of "jaggery", particularly for the sweets made at the festival of *Divali*.

Professor Tara Das Gupta, a native of India, has been a member of the Chemistry Department of Jamaica's campus of the University of the West Indies (UWI) for 20 years. "Professor Das Gupta, does your wife cook with jaggery?" I asked. "She likes to, when she can get it." I made him aware of the fact that India's jaggery is much the same as Jamaica's Head Sugar, and that I was trying to find a farmer who makes it. He enthusiastically exclaimed, "If yuh fin" 'im, mek sure yuh bring some fe me."

In response to my search, a former schoolmate agreed to take me to one of the few remaining Head Sugar artisans. Mr. Leopold Maye, proved to be an inspired Jamaican small-farmer-entrepreneur. A tour of his facility was a walk down memory lane. He is the third generation practitioner of the art of Head Sugar making, his father and grandfather having paved the way before him. His yard is strewn with cane-crushing devices that could be a timeline in the evolution of these instruments. One that would have been powered by an animal walking endlessly in a circle, was reminiscent of Mr. Thyme's sugar mill of my childhood. Another, equipped with sprackets, ratchets and chains suggests the advent of the Industrial Revolution.

The comparatively massive cane crusher currently in use, bears testimony to Mr. Maye's mechanical acumen and ingenuity. The size of the fly wheel clearly indicates that it should be connected to the driving mechanism by a four inch wide belt. However, Mr. Maye's driving mechanism is a two stroke engine cobbled together from a little tractor. And, instead of a four-inch-wide belt, there is the ubiquitous black, half-inch belt that you will see if you look into your car's engine. Ignition was effected in the old fashion way, by use of a draw cord to get the pistons moving.

There was no need to cut the stalks of cane into two-foot lengths, as with Mr. Thyme's puny machine of my childhood. The long stalks of sugar cane were fed manually into the Rube Goldberg machine, and the emerging juice was collected into a 20 ft long pvc pipe that emptied into the first of three huge, saucer-shaped cast iron cauldrons in the boiling house 20 yards away.

Mr. Maye's boiling house (Fig. 1.2) is a scaled-down version of the 1840 original from *The Illustrated London News,* captioned "THE INTERIOR OF A SUGAR BOILING HOUSE". In the sketch which is reproduced in Fig. 1.1 we can see that there are six boilers on the left-hand-side whereas Mr. Maye's House had three (Fig. 1.2). And instead of seven slaves engaged in the process, he had only himself. But the basic concept remains the same.

Contrary to the practice at Mr. Thyme's mill (Sect. 1.1), the de-juiced cane stalks (bagasse) are not used for fuel. According to Mr. Maye this causes ash to collect in the product! Instead he used bamboo. This was not only eco-friendly, but an enterprising decision. Bamboo is widely used for scaffolding by rural Jamaican builders, and when they have finished, he collects the discarded bamboo, in obviously a win-win arrangement for the artisan-farmer and the builder.

During the evaporative process, the increasingly thick liquid was transferred manually from the first to the second, and thence to the third cauldron. This was done by means of a bucket, nailed to the end of a 10-ft long pole. The decision about when to do these transfers clearly requires skillful judgment of the operator.

The steaming, boiling, bubbling cauldrons threw up a vast amount of froth, and Mr. Maye skimmed this off using a perforated ladle, also attached to a 10-ft pole. However, the thick froth could entrain valuable syrup, and so the skimmed froth from the third cauldron was added to the second, and that from the second was added to the first. In this stepwise process, the froth from the solution with the highest concentration of sugar (i.e. the third cauldron) is eventually transferred to the first cauldron, containing the incoming juice, which has the lowest concentration of sugar.

Two of the slaves in Fig. 1.1 are using 10-ft long ladles, which shows that the practice goes back to the days of slavery. The knowledge that the froth of the last

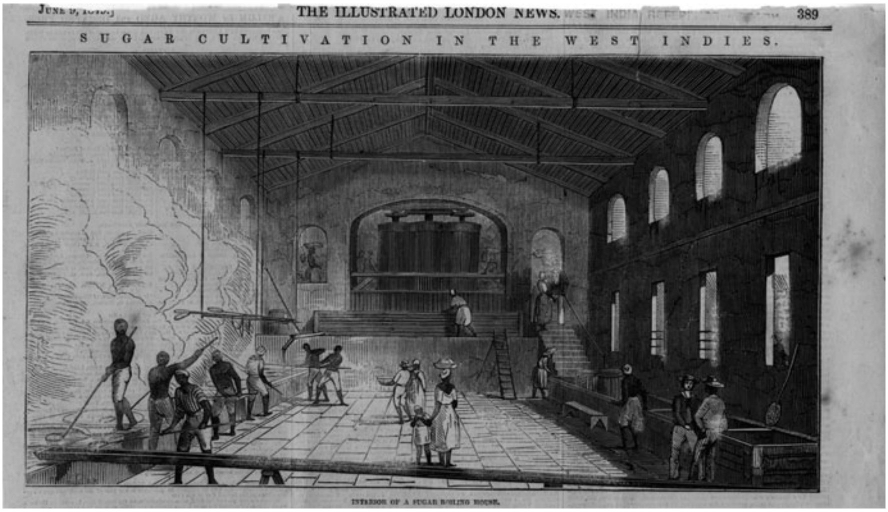

Fig. 1.1 The Interior of a Sugar Boiling House (1840) from the *London Illustrated News*. (Courtesy of the National Library of Jamaica)

Fig. 1.2 Mr. Maye's Boiling House (2010) From *top left*: (1) the stalks of sugar cane are fed manually into the teeth of the crusher; (2) the resulting juice is funneled through a pvc pipe, and is strained into the first boiler; (3) steam from the three boilers can be seen. From *bottom left*: (4) the highly concentrated juice in the third cauldron; (5) syrup is allowed to cool in the trough while maintaining constant stirring; (6) the four styrofoam cups contain the solidified "head sugar". The three plastic cups contain "wet sugar" where the solid is dispersed in more molasses

cauldron is valuable and so should be recycled, has clearly been handed down through many generations.

Interestingly, the process is reminiscent of the liquid/liquid extraction strategy that is taught to chemistry and chemical engineering undergraduates and is widely practiced on an industrial scale. In Mr. Maye's case, however, success of the liquid/liquid extraction process relies on his skilled eyes, rather than on sensors in the liquid that measure the concentration of the solution at various stages.

Eventually the plop, plop, plopping in the third cauldron became more and more pronounced, signaling that crystallization was imminent. To facilitate this critical process, a suspension of white lime (calcium oxide) was added – ostensibly to prevent the sugar crystals from clumping together. However, another plausible reason is that the calcium oxide neutralizes saccharinic acids that are produced during thermal decomposition of sugars. These acids are responsible for the slightly bitter taste of molasses; but this is notably absent in Head Sugar.

The thick brown goo was poured into a flat trough to cool. This is seen in the fifth picture of Fig. 1.2 (See also right-hand-side of Fig 1.1). Constant manual stirring, scraping, and folding was maintained to ensure homogeneity, and at a critical stage, recognizable only to him, Mr. Maye ladled the warm, thick, caramel colored syrup into styrofoam cups. That his timing was indeed exquisite, could be proved by pulling one of the drops that spilled on the table. I tried, without success, to stretch these drops; instead they snapped. This result provided circumstantial evidence of the high quality of the product – according to Mr. Maye (Fig. 1.3).

I fulfilled Professor Das Gupta's request, and his wife was so impressed with the Head Suga' that she asked for three containers, on my next visit. Interestingly, they found that Head Suga' was not as hard and compact as jaggery, this being a great advantage for its use in cooking.

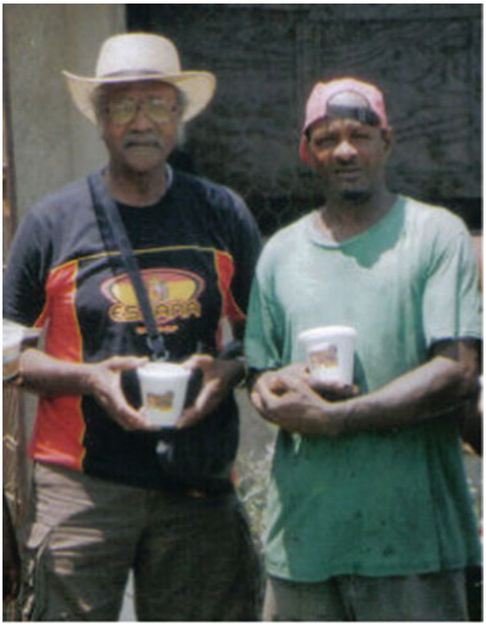

Fig. 1.3 The author and Mr. Maye display cups of Head Sugar in July 2010.The label reads "L. Maye Co. REAL COUNTRY SUGAR HEAD, Summerfield, Clarendon, Jamaica, Tel. 1(876) 846–8483; cell 1(876) 4010373

1.2.3 Tate & Lyle and Jamaica

The name Tate & Lyle is certainly well-known to most Jamaicans of my generation. For some it was associated with the sugar they purchased at the grocery shop (for there were no supermarkets in those days). But popularity also came from the West India Sugar Company (WISCO), a subsidiary of Tate & Lyle, that owned and operated some of the island's sugar factories. WISCO's connection to sports was visible and treasured. The playing fields at their Estates were immaculate, and their teams comprised skilled players in what seemed to be sinecures. School boys welcomed the opportunity to play on their fields, and although they would almost certainly lose, they would be subsequently compensated with a sumptuous repast served in the Estate's posh Club House.

Chapter 2 of Sheridan [4] is entitled "Sugar: The inseparable companion of tea." How interesting that the "inseparable" companions should be tea from East India, and sugar from the West Indies – since Columbus had "discovered" the latter while looking for the former!

In the 1700s Britons used more than two times the amount of sugar that France did. This "sweet tooth" required that the commodity be available throughout Britain. As a result, the number of houses that refined the "unrefined" product from the Islands increased dramatically, London alone having eighty. The growth in refineries of sugar brought a rise in British standard of living with a broad uptick in prosperity, leading to "an age of relative plenty for the working class" [4] during that period.

In the mid 1850s, the families of the Tates and the Lyles entered the sugar refining business. The affection of the British for sweets brought immense and rapid prosperity to the enterprise. The grandeur of London's Tate Gallery comes to mind. The companies merged in 1921, and Tate & Lyle grew into arguably the world's leading sugar refiner. Sugar Estates in the colonial islands of the British West Indies had supplied the material to be refined for years; but there were looming problems at the source. For example, in Jamaica, an island of only 4,300 square miles, there were about 800 sugar estates in 1773; but by 1965 that number had plunged to 18. The same trend was mirrored in other West Indian Islands owing, in part, to the emergence of sugar beets, which could be grown in the temperate zone, as an alternative source of sugar.

This decline in the supply of raw material, prompted the giant sugar refiner to become a more direct participant in the actual production, not just the refining, of sugar. So, in the 1937–1938 years, Tate & Lyle, through its subsidiary, the West Indian Sugar Company (WISCO), took over several sugar estates of the British West Indies, two of which were Jamaica's largest, Frome and Monymusk (Fig. 1.4).

According to Patrick Henry in an article entitled *The Carribean - Tate & Lyle's Changing Role,* "Tate & Lyle — now had a secure foot hold in all aspects of the sugar industry – a vital ingredient to a rapidly expanding Tate & Lyle." And Ian Sangster, a purveyor of fine liquers, noted in a 1973 review, that it would be difficult to exaggerate the importance on the Jamaican sugar industry of this giant company

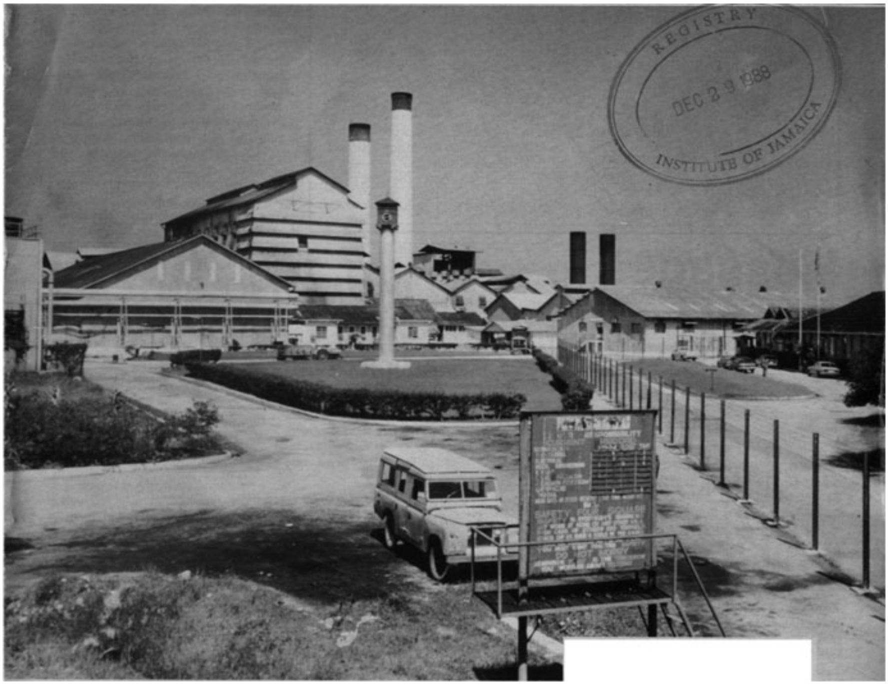

Fig. 1.4 Frome Estate (1988) (Courtesy of the National Library of Jamaica)

with its world-wide sugar experience. Indeed, in the 20 years that followed Tate & Lyle's acquisition of some West Indian sugar estates, a fourfold increase in sugar production was realized.

However, Tate & Lyle's role in Jamaica was much more systemic than that of a narrow sugar producer. Reversal of the downward spiral of sugar production required greater efficiencies which invariably meant mechanization wherever possible, which invariably led to a decline in the need for manual labor, which inevitably threatened 300 years of sugar production that had been driven by the manual labor of slaves and their descendants. This was true not only in Jamaica, but in other colonies, as they then were, of the British West Indies. Wide-spread Caribbean labour unrest escalated.

By coincidence, events in the United States had a timely influence. The fury of John L. Lewis, the bellicose president of the United Mine Workers of America, was reported in the Jamaican newspapers, and the benefits that he was able to wrest for lowly coal miners showed that trade unions could be effective in improving the lot of common workers. These events undoubtedly inspired West Indian trade unionists, among whom, the names of Uriah Buzz Butler of Trinidad and Tobago, Grantley Adams of Barbados, and William Alexander Bustamante of Jamaica, are seared into my childhood memory, right beside John L. Lewis.

A historically significant unrest surrounded the 1938 building of the Frome factory in Jamaica. This was designed to improve mechanization and, by corollary, decrease manual input. William Alexander Bustamante considered this an insult, and greeted the event with a series of orchestrated riots. The police and Military of the then colony were called out. Although Bustamante was jailed for his affront, the events culminated in the formation of the Bustamante Industrial Trade Union (BITU). Jamaica's first trade union was therefore a direct outcome of the incipient changes in sugar production at the hands of Tate & Lyle. Bustamante was charismatic, furious and loud. A foil to his menace was provided by his erudite, Oxford-trained cousin, Norman Washington Manley, an iconic barrister who provided early legal support.

But in time, the Bustamante Industrial Trade Union gave birth to its own political arm, the Jamaica Labor Party which, in spite of its name and underpinnings, was seen as politically conservative. His cousin Norman Manley started the Peoples National Party (PNP) which was seen as progressive. Subsequently, the PNP developed its own trade union, the National Workers Union (NWU), a prominent leader of which was to be his son, Michael Manley.

The party/union synergy, JLP/BITU and PNP/NWU, thus became embedded in the political fabric of Jamaica. The resulting two-party system, dependent on union/party fealty, which had its origins in Tate & Lyle's 1930s efforts to energize sugar production, still persists in the island's democratic processes. This is nicely summarized in a 1976 article to *Sugar Digest* by Noel Donaldson, then general manager of the Frome sugar estate. "It can therefore be said that Frome played a key role in shaping the political system in Jamaica, and understandably so, as it was to become one of the largest single export earners at the time, and therefore had great influence on the economy of Jamaica".

In an effort to dampen the trade union furor, Tate & Lyle instituted profit-sharing schemes, in 1961, with the help of one of the trade unions. A requirement of the schemes was "regular attendance at work". This bold insinuation speaks volumes about the West Indian laborers' proclivity for passive resistance. In any event, in 1965 the democratic process brought the "other" union/party to power, and it called a halt to these profit-sharing schemes.

As noted above, the sugar estates maintained excellent sport facilities. In this regard, Frome and Monymusk set the standard, and it should come as no surprise that many of the Jamaican (and West Indian) athletic superstars had their start on teams sponsored by the Tate & Lyle's Caribbean subsidiary, West India Sugar Company (WISCO). For example, the legendary cricketers Alfred Valentine, Reggie Scarlett, and Roy Gilchrist honed their skills on the estate's cricket pitches.

By and large there is much evidence that Tate & Lyle's West India Sugar company (WISCO) provided a wide range of services including creation and maintenance of roads in and around the factories, subsidized houses for its workers, scholarships at local schools to promising students, these being indicative of "good corporate citizen" behaviour.

West Indian sugar production faced increasing pressures from countries such as Australia where mechanized sugar cane cultivation flourished, and even moreso from the United States and European sugar beet industries. However, additional pressure came from an unexpected source. The surge in world requirement for aluminium in the 1940s brought companies, initially, from Canada, Britain and the USA, to tap into Jamaica's high grade bauxite, the source of aluminium. The result, as far as labor was concerned, was exhilarating, because enterprising workers could now upgrade their station in life, by becoming skilled factory workers, and thereby escape from the toil of sugar cane cultivation. These choices, depleted the talent pool available to Tate & Lyle.

But rapid political changes in the West Indian islands were even more determining. Independence ended colonial rule, leaving each island of the original British West Indies to (try and) chart its own destiny, rather than rely on dispatches from Whitehall.

However, rum, a major by-product of the sugar cane industry is immune from the sugar beet incursion because the molasses obtained from sugar beets is not suitable for producing good rum. Thus, while Tate & Lyle's factories focused on sugar production, Appleton Estate, independently owned by Jamaica's J. Wray & Nephew, emerged as a producer of excellent rums, enhancing the image of Jamaica as the place "where de rum cum from"

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Chapter 2
Growing Up In Jamaica

2.1 Some Things I Learned From My Diabetic Father

2.1.1 My First Chemistry Experiment

My stepmother was still alive when I made my first contact with chemistry, so I must have been less than 7 years old. The memorable event was watching my father test urine, his or that of sundry other folks who had “sugar”, as diabetes was known in the rural hills of Jamaica where I grew up. This and other such community services were liberally dispensed by “Teacher”. I do not recall if these measurements were duly recorded, but my father was such a meticulous diarist, that he would certainly have noted the date and time of his, or the subject’s test, and whether the result was negative or positive.

In fact my father was meticulous about whatever he did, such as preparing for the experiment. First, the required apparatus was laid out on a white towel. The spirit lamp was filled with the purple colored fluid, and the wick was put in place. A test tube and the leather holder, which he had made, were set aside. The wick of the spirit lamp was lit, the test tube was charged with Benedict’s solution to one-third its length, and then placed in the leather holder. Urine, his or the subject’s, previously collected in an enamel chamber pot, was brought forth. An eye-dropper with a rubber suction bulb was used to transfer a few drops of urine into the test tube and heating begun. The translucent blue solution soon started to boil, and sometimes a whitish solid formed. This was a good sign and meant that the “sugar” was not too bad. But woe be it, if a copious red-brown deposit formed for that meant that the “sugar” was too high.

It was some 15 years later before I understood the details of my father’s experiments. First, he had obtained the apparatus at the Drug Store operated by Miss Bailey, the nosey “druggist” in the town of Christiana, 2 miles from the Teacher’s Cottage at Bryce, our village. The fuel for the lamp, also purchased from her, was methylated spirits, which was actually nothing more than ethyl

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_2,

alcohol, adulterated by addition of methanol and a purple dye, so as to discourage people from drinking it.

Miss Bailey also prepared the Benedict's solution, and she told me that the blue color was due to "blue stone" with which I was familiar, since it was one of the ingredients of the spray that was applied to banana trees to combat leaf-spot disease. I later learned that the proper name for "blue stone" was copper (or to be more precise, cupric) sulfate.

How did "sugar" cause the solution to change from blue to red-brown?

Well I first had to learn that the "sugar" in question was not the same as the substance with which I loaded up my cocoa, and which my father avoided like the plague. He sweetened his coffee with a little white pill which he called saccharin.

"Table sugar", or sucrose, is actually a combination of two other sugars, glucose and fructose. The latter two are called monosaccharides and so sucrose is called a disaccharide. If sucrose is tested with Benedict's solution, it will give a negative result; for reasons that I will explain shortly. However, when sucrose is ingested, it is cleaved by a group of and in normal people the released glucose and fructose are used to supply energy. Any unused glucose is stored for future use as a complex sugar called glycogen and, regrettably and visibly, as fat.

But in order for glucose to supply energy, it must enter the cells where it will be broken down. Entrance to the cell is facilitated by a hormone called insulin which is secreted by the pancreas.

Diabetes is a condition where there is a problem with insulin doing its job. In some people, known as Type 1 diabetics, the pancreas does not produce any insulin at all. This condition occurs mostly in children and was formerly known as juvenile diabetes. With such diabetics, insulin has to be administered so that the subjects can derive energy from the food they eat.

Type 2 diabetes was known formerly as adult-onset diabetes, because it occurred in middle-aged people owing sometimes to heredity, but also because of obesity and an inactive lifestyle. In Type 2 diabetics, the cell is resistant to the action of insulin, and so the pancreas puts out more insulin to try and overcome this resistance.

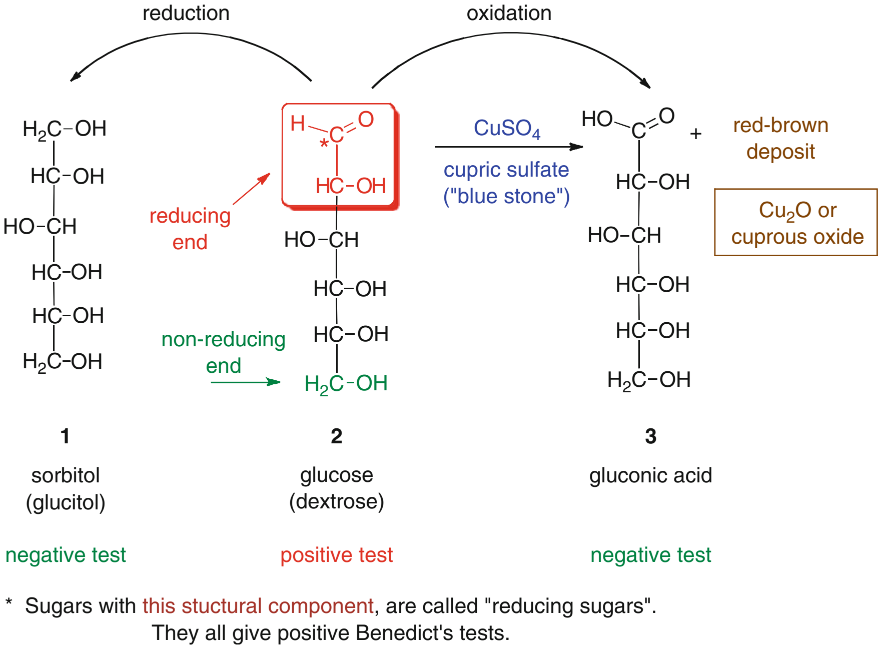
But this condition cannot be allowed to continue, because high levels of glucose moving through the body could result in multiple disorders, including renal failure, blindness and, in extreme cases, hard-to-heal wounds in the extremities, that sometimes lead to amputations. Because of this, insulin has to be injected to augment the naturally produced levels, so as to get rid of the excess glucose.

Notably, exercise also helps to burn up the excess glucose.

The usual way to test for glucose in chemistry laboratories involves the use of Fehling's solutions A and B. However, the urine of diabetics frequently shows high levels of a protein called creatinine, which interferes with Fehling's test. Benedict's solution, used by my father, was therefore developed to overcome this interference; it has the additional advantage of being stored as a single solution.

Now what about the chemistry that was taking place in my father's experiment?

Two of the most fundamental reactions in nature are oxidation and reduction, and glucose is able to undergo both. Glucose (**2**) known also as baby sugar or



Scheme 2.1 Benedict's Solution contains blue copper sulfate, which converts glucose to gluconic acid, with concommitant formation of solid, red-brown copper oxide

dextrose, is a ready source of energy and is a major component in drinks that are consumed by athletes for a ready boost of energy. Reduction of glucose (**2**) gives glucitol, which is more commonly known as sorbitol (**1**). Sorbitol is also sweet but its sweetness is about 60% of that of sucrose. And because it is metabolized very slowly, it has value as a low calorie sweetener and is a common ingredient in "sugar free" candy. However, caution is required because flatulence is an undesirable side effect of its use; and it has also been linked to *irritable bowel syndrome*.

As seen from Scheme 2.1, sorbitol (**1**) does not have a "reducing end", and so it does NOT give a positive Benedict's test.

In the reaction with Benedict's reagent, glucose is oxidized to gluconic acid **3**. In the process, the blue cupric sulfate is concomitantly reduced to cuprous oxide, which is a red/brown solid.

2.1.2 *Periwinkle: Diabetes* Versus *Cancer*

Today, I am a type 2 diabetic, as are/were two of my siblings; and as I reflect on my father's battle with the disease, I am filled with admiration for his discipline and amazement at his foresight. He did not use insulin, because in the late 1930s (I was born in 1934) it was far too expensive for a school teacher's salary, and in any event we did not own a refrigerator in which to store it. There was no electricity; but some of our better-off neighbors had kerosene-powered refrigerators.

In those days, insulin was obtained from the pancreas of pigs and cows, but human insulin is now produced in vast quantities by genetic engineering.

My father's preferred medication came from a tall glass of a tea brewed from the leaves of the periwinkle plant, the botanical name of which is *vinca rosea.* The decoction was astringent and excruciatingly bitter, which led me to wonder if the rationale behind its use was that the sugar in the blood would be countervailed by the bitter principle in the periwinkle tea. However, I have learned that this home remedy for diabetes is also widely used in the Indian subcontinent; and so it probably came to Jamaica with the Indian indentured laborers, who were brought to the West Indies by the British colonial powers following the abolition of the West Africa slave trade.

The wide-spread use of periwinkle extract for controlling diabetes in Third World countries was bound to attract First World scrutiny. According to *Wikipedia*, the story begins as follows:

"In 1952, Dr. Robert Noble received an envelope from his brother Dr. Clark Noble containing 25 leaves from the Madagascar periwinkle plant (Vinca Rosea). It was sent from one of Clark's patients in Jamaica, who had said that a periwinkle tea was being used in Jamaica for diabetes treatment when insulin was unavailable".

The author is not able to vouch for the accuracy of the above quotation, but it is entirely plausible since the periwinkle plant grows worldwide.

What can be gleaned for the scientific literature is that in 1955 Dr. C. T. Beer, a medical researcher at Canada's University of Western Ontario disclosed, in a British publication, that a crude extract from periwinkle (obtained from a colleague at the University of Miami) caused "a fall in the circulating leukocytes (white blood cells)—in a—rat"—. This observation suggested a possible treatment for leukemia, a health disorder where white blood cells increase abnormally.

Could the periwinkle extract prevent this abnormal increase of white blood cells?

Three years of in-depth study with purer material followed, and Dr. Beer published an update, co-authored with two of his colleagues (Drs. R. L. Noble and J. H. Cutts), showing that "this substance can readily inhibit the growth of a number of animal tumours."

Not surprisingly the anticancer potential attracted immediate and intense scrutiny, and in 1959, Dr. Beer collaborated with four scientists from Lilly Research laboratory (Eli Lilly & Co.) to isolate the active ingredient, which came to be known as *vinblastine.*

Interestingly, another team from Lilly immediately disclosed that a second active agent was present – and this came to be known as *vincristine.*

Independent work at Eli Lilly on the periwinkle plant (*vinca rosea)* confirmed the absence of anti-diabetic properties. Fortunately, my father did not put all his eggs in the periwinkle basket. He took other steps to control his sugar. He used his homemade dumbbells every morning, at a time when grown men in Jamaica ridiculed exercise, and were ridiculed for exercising. We did not own a car – nor a bicycle; but walking two miles to and from Miss Bailey's Drug Store posed no problem for him, even into his advanced years. He did not drink alcohol – a flagrantly anti-social practice in Jamaica "where the rum comes from".

As far as his diet was concerned, he eschewed the starchy "ground provisions" of yams and sweet potatoes, and the fatty meats, fried in coconut oil, now known to be bad-for-you, that are staples of the Jamaican diet. He replaced these with steamed fish (ugh!), cabbage (ugh! ugh!!) and okra (yuk!!!), and a tasteless, full-of-water vegetable known as cho-cho, available as chayote squash in North American supermarkets.

I am mystified as to how he knew that whole wheat (brown) bread was better for him, than the heavy, hard dough bread, made from refined flour that Jamaicans will die for. His weekly rations of two loaves of brown bread were sent once a week from a bakery in Kingston, 60 miles away.

Because of these multifarious methods of control, my father was trim and lived until he was 76, which at this death in 1957, was a ripe old age for a Jamaican.

That "belief is better than cure" is a well-known aphorism. Perhaps "belief" is a bigger part of the healing arts than the exponents of "cure" are willing to acknowledge. Fortunately, my father never knew that the periwinkle tea was of no anti-diabetic value, or that the Benedict's test was fraught with problems. For one thing, the threshold for a positive Benedict's test is so high, that the absence of a red-brown deposit was no cause for comfort. For another, the positive test would have been given for ANY analog of glucose that had the "reducing end" segment highlighted in structure **2** (Scheme 2.1).

Diet and exercise were probably doing it for my father.

2.1.3 Saccharin: His Sugar

Eschewing sweet foods condemned my poor father to miss out on the sweet potato puddings, corn pone, bulla cake, sugar buns, and most of all, sweetened condensed milk that the rest of us feasted on. My sweet tooth would demand four teaspoons of sugar in my beverage. One saccharin tablet was enough for him; although it was very expensive as compared to brown sugar, the poor man definitely deserved a break.

(See Sect. 5.1.4 for further information about Saccharin)

2.2 Schooling

2.2.1 Primary

The Jamaica of my youth was still a British colony, and so the British educational system was followed – more or less! My primary school education was at Bryce

Elementary, of which my father was "Head Teacher". There were six grades, and the age of graduation varied, depending on when the student entered Grade I, whether they skipped a grade or two, or had to repeat a grade or two. For those who made it all the way through, that being no easy task, the opportunities were stark.

For the brighter, poor kids, the Pupil Teachers' (PT) program was the most accessible. There were three grades of PT exams, I, II and III. My father and some other teachers gave after-school lessons to the aspirants, preparing them for the PT exams which were administered once a year. Some of these aspirants worked at the school as assistants to the assistants of the assistants, whereby they burnished their skills at imparting knowledge to the next generation, with the help of a few cuffs now and then to accelerate the learning process.

The long-term goal of Pupil Teachers was to gain acceptance to one of the island's Teachers' Colleges, Mico for men, and Shortwood for women. These were (are) highly reputable institutions. Their distinguished graduates include many luminaries who, after Jamaican independence, became Ministers of Parliament, Speakers of the House, and even Governors General to represent Her Majesty.

A far less traveled post-Primary School pathway was to go to Secondary (High) School. It would be many years later, as an undergraduate at Queen's University in Canada, that I had to confront the fact that only privileged children went to High Schools in the Jamaica of my youth.

This insight came as a result of a public lecture that a Queen's Professor gave about his sabbatical year at the University in Jamaica. Given the fact that my father couldn't afford a car, a bicycle or a radio, and many parents of my schoolmates had to borrow money to pay the High School fees, I felt that the Professor's research may have been conducted in the comfortable confines of the University's Common Room, instead of in the rural villages.

But shortly after listening to the lecture, I was forced to conclude that the Professor was right. This was because when I was introduced to a Jamaican student from another Canadian University, we soon found that we had at least one common acquaintance. Students of that era, therefore had about one degree of separation between our High School cohort. Ours was therefore a highly distilled sector.

Furthermore, my father may have been too poor to buy a radio, a bicycle or a car, but he did find the money to buy a set of *Cassel's Books of Knowledge* into which my sister Pixie and I would immerse ourselves after supper, whetting our appetites to visit "strange" lands, a yearning that we both fulfilled as adults. In addition, we had a piano, a violin, and a harmonium organ; and we all had to learn how to play an instrument. Probably we were poor, but we were not uncultured.

2.2.2 *Music* Versus *High School*

My father retired as "Head Teacher" of Bryce Elementary School in December of 1945. I was then 11 years and 10 months old and therefore ripe for secondary schooling, according to the British tradition. In those days there was no secondary school nearby, so I would have to be sent to a boarding school. The previous year my sister, Minette (Pixie), had won a scholarship to St. Andrew's High School, arguably the island's elite Girls School. I may have also taken a scholarship exam in the hope of following in her footsteps. But if I did, it did not register with me, since I cannot remember the experience. In any event, I certainly didn't win anything.

The secondary school year consisted of three terms of roughly three-and-a-half months each. And so in January 1946, I was shipped off to Excelsior School in Kingston as a boarding student. At that time, the School was a fledgling institution, led by Mr. Wesley A. Powell who would blossom into one of the island's most visionary educationists. Thus today, Excelsior is a major multi-functional mega institution that belies the humble beginnings, into which I was delivered in 1946.

The cramped quarters, then on North Street, were adjacent to the Seventh Day Adventist mega-church, with which Excelsior was affiliated – or so it seemed to this 11 year old. I do not recall being subjected to any religious indoctrination; but then that was the least of my worries. School children look forward to the weekends – but I did not. The Sabbath for Seventh Day Adventists begins on Friday night, which meant that play and frolic on the Sabbath was forbidden, even for us non-believers. Much more distressing was that the prohibition extended to the kitchen, and so for the next 24 h, survival would require that we eat cold food.

And what was worse, they eschewed pork.

Whether or not these hardships played into my father's decision, I do not know. But to my delight, for the next term I became a day student, and was boarded along with my sister, with a wonderful family. But if the poor man could have been blessed with foresight of events for the upcoming 3 months, he would have kept me at home. He would soon have to do so anyway.

The route from my boarding house to Excelsior School took me past Bryant's Piano Studio, and I soon discovered that this studio was a favorite gathering place for Jamaica's elite piano players, who plied their trade in the thriving tourist industry. My talent at the piano was on display early in life, even before formal lessons (from my father) had commenced at age 6. The piano styling's of the pianists to whom I was listening at Bryant's studio, held out promise that I could graduate from "Smallwood's piano tutor", with its arid pieces, such as "The Bluebells of Scotland". Instead I could indulge in sumptuous ballads, elegantly played.

And so Bryant's Piano Studio soon proved to be much more alluring than the Latin which Mr. Echeverier was trying to teach me at Excelsior School. I therefore excelled in music appreciation, but came second to last in my class.

My poor father! Here he was, a retired school teacher, living on a teacher's pension and trying to pay my school and boarding fees. Well, he responded by pulling me out of Excelsior, bringing me home, and sending me back to Bryce Primary School to which I had said goodbye 8 months earlier. He would park me there for the last 3 months of 1946, while he figured out what to do with me. This experience, though well deserved, was a crushing humiliation, because after seeing the bright lights of Kingston, the kerosene lamps of the rural village of Bryce were a drag.

One fateful day, I decided to skip classes for the afternoon session. This was not uncommon. Usually, I would hook up with Baba, my neighbor, and go bird shooting in the nearby bush. But this day I headed home, expecting that my father would be out and about. No such luck. “Why aren’t you at school” he demanded. “I am having pains in my leg”, I lied. Instead of being angry, he seemed worried. “This is not the first time you have complained of these pains—Maybe I should take you to the doctor tomorrow”.

Yippee!! No school for me tomorrow, I rejoiced.

Dr. Tomlinson did a thorough examination, and pronounced that I was suffering from acute appendicitis! “Take him to the hospital right away” he instructed my father.

Dr. V. R. Robb, the island’s legendary, avuncular country physician/surgeon operated on me the next day. He made me a present of my appendix preserved in a fluid – probably formalin. He explained in detail what had gone wrong with the worm-like thing. But as I had no idea what a good appendix was supposed to look like, I did not appreciate what was so bad with mine.

I remained in hospital for over 2 weeks, because it took that long for the three-inch wound in my side to heal. It did not help matters that I would not stay still. On one occasion, I went outside to help push a stalled car, much to the annoyance of the charge nurse, who cuffed me a few times to emphasize her displeasure.

After that I was obviously too weak to return to Bryce Elementary school. My contrived, delicate condition, and prolonged recovery, would continue to serve me well into the immediate future.

My long-suffering father had not given up all hope. While I was luxuriating in my recovery, he was looking for another boarding school. And he found another fledgling one, just like Excelsior, but not in Kingston, and happily not affiliated with Seventh Day Adventists. This one was located in the far hills of the neighboring parish, Clarendon, near the peak of the Bull Head mountains, in short, behind God’s back. And the clincher was that there was not a piano studio for miles around.

2.3 Clarendon College: Student AND Teacher

And so I started at Clarendon College in January 1947. I was to spend the next 9 years at this school, four as a student, and then five as a junior teacher.

As a “grub”, hazing was to be expected, based on rumors we had heard about the British boarding school tradition. It was one of the best ways to build character, we were told. Some lucky grubs were given a pass. For example, fellow grub, Boyd Neita was granted exception by upper classman Baz Dawkins, because he had a beautiful sister. No one seemed to know about MY beautiful sister, so I had to devise my own exemption from hazing. With the three-inch scar on my belly as incontrovertible evidence that I had just had a near-death experience, (who could quibble about a month or two), I needed time to recuperate. It also helped that I was one of two students who could play the piano well enough for the Saturday night dances. I was therefore not only delicate, but valuable.

I am reflecting upon those days, more than 60 years later, at a time when departing President George W. Bush used to hail "No Child Left Behind" as one of his major pieces of legislation. The success of that edict was determined by regular tests. The premise was that if the teachers taught well, the children would test well. By corollary, if the children tested poorly, the teachers were clearly incompetent.

Since in my 9 years at the school, I was both a student and a teacher, I can certify that the postulate and its corollary are fatally flawed.

We were tested every so often, the apparent purpose being to separate us into streams of bright, less bright etc. There was even a "Remove" status, which, it seemed, meant that the students could be moved down, up or out. But I don't remember that any one lost any sleep over his/her status.

This was probably because the really important exams came from England, and were based on a curriculum that was designed to ensure that in the British Commonwealth upon which, in those days the sun never set, colonial subjects would be brought up to par. So it is rumoured that students from the islands of the British West Indies, joined their cohort in Hong Kong, Ghana, India etc., and sat down to write the same set of exams that had been prepared by Cambridge University. The answer-books were sent back to Cambridge for grading, and some months later the Jamaican results would be published in *The Daily Gleaner*, the island's major newspaper.

My miserable record from my 9 months at Excelsior School notwithstanding, I was placed in the middle school at Clarendon College. This meant that at the end of my first year there, at the age of 13, I would sit for the Cambridge Junior School Certificate exams in December of 1947. My favorite subject then was geometry, and I well remember that I was about to write the exam, when I received a telegram from my father telling me that my maternal grandmother had died.

In view of the exams, there was no question of going home for her funeral. Miss Shattie had been my savior and caretaker in multiple ways. She probably had a special place for me, because her only daughter, my mother, had died when I was 9 months old. As I cried at the news, the Headmaster, Mr. Stuart, tried to console me, but also counseled that I should celebrate her memory by giving a good account of myself in the exams.

And I guess I did, in geometry for sure, since I got an A at the Cambridge Junior Certificate level. I probably failed a few subjects, but as far as I can recall, there was no penalty for such failures. I certainly did not have to repeat a year.

Two years later, I wrote the Cambridge Senior School Certificate for which there were three passing grades, first, second, and third. I learned from the published results in *The Daily Gleaner*, that I had "scraped" through with a third.

At the elite schools in Jamaica, this poor performance would have had dire consequences for this 15 year old boy. At those schools, a first class grade would have been required to proceed to the next level, which was the Cambridge Higher School Certificate, 2 years down the line.

Fortunately, Clarendon College was not one of those elite schools. Entry to those institutions was easiest if you were white, next if you could "pass" for white, next if you were from a wealthy family, and finally if you were black and bright. I failed to qualify on every count. I really did not know whether I was bright or dumb. I would not have described myself as being "lazy". In fact I recall that I was always busy. "Uneven" might be better description. I was fully engaged in subjects that I liked (biology and geometry), but fully disengaged in others (literature and history).

Because of the less-than-elite status of Clarendon College, low achievers with third class Cambridge School Certificates were allowed to proceed to the next level. And so in keeping with the British system, I embarked upon 2 years of intense study of a few chosen subjects. My choice was limited to what was available – botany, zoology, economics, and geography. These subjects were presented in rigorous detail, certainly the equivalent of freshman standards at some North American universities.

Our teachers for economics and botany were graduates of British universities, and both were eccentric. Miss Ashbourne, a product of the London School of Economics, had spent the war years in England, and having lived through the London blitz, sometimes showed evidence of (what I now realize as) post traumatic stress disorder (PTSD). To our adolescent, insensitive, irreverent amazement, the shaking, shivering, and shimmying, as she spoke, were greeted with gales of laughter.

The botany teacher was the Reverend Mr. Leonard Fountain, who held a Master of Arts degree from the University of Edinburgh, Scotland. A class-mate recently described him as an original hippie.

It is said that Scotsmen traditionally do not wear anything beneath their kilts. Mr. Fountain extended that tradition to his baggy short pants. And because his favorite lecture style was to place one foot upon a chair, the view from the front row was very revealing – especially to the girls, who flocked to the front of the class, ostensibly because of their interest in botany!

As far as the boys were concerned, that revelation could be had on any given Saturday morning. Mr. Fountain deplored the fact that most of the boys could not swim. And so every Saturday morning, he collected a bunch of male boarders, walked a mile or so to a lagoon, where everyone removed shirts and pants, and since young boys in those days did not wear underpants they, along with Mr. Fountain, all swam naked.

Mr. Fountain was obviously encouraged by the results of these swimming lessons, because he entered some of his newly minted swimmers in the All Island Interschool's Swimming competition. This event was held at Bournemouth Club, then one of the island's posh resorts, which sported an elegant pool. But this was a bewildering experience for country boys, unaccustomed to wearing swimming trunks, and totally ignorant of lanes. Jumping off the platform into the pool was novel, for they were accustomed to launching themselves from the lagoon's embankment with a mighty belly flop.

Luckily, I never made the team.

Our teachers for the other two subjects, zoology and geography were not university graduates. Both had been trained at Mico Teachers' College and were busily upgrading their credentials**,** one of them to eventually become a School Principal at another High School, and the other to enter medical school at Howard University in the United States. Indeed they were both studying for the very same exams that they were supposedly preparing us for! Actually, the zoology teacher was repeating the exam because he had failed it the previous year.

This situation did not seem as perilous then, as it now appears in retrospect. We may have been at a disadvantage by having teachers so limited in the compass of their subjects; but luckily we did not know it. We simply found out what we had to learn, and went ahead and learned it. It was in a sense, a survival strategy. We literally read various text books that were used at the elite schools, and disgorged the newly acquired information to one another. The happy result was that of the eight of us who sat the exam in 1951, seven gained Cambridge Higher School Certificates.

All of us in that class were/are greatly indebted to *all* our teachers – even those who were limited in their subject. Their encouragement was never withheld, and they worked very hard on our behalf. Since this was a boarding school, they were always within easy reach, 24/7. We even profited from their shortcomings, for our circumstances forced us to learn how to learn, and in so doing, came to appreciate the aphorism, attributed the Albert Einstein, that "an education is what remains, after you have forgotten everything that you were taught in school".

And so that remote, under-staffed country school provided me with an education that has continued to serve me well for over 60 years.

2.3.1 "If You Come To a Fork in the Road, Take It" (Yogi Berra): Chemistry By Happy Default

The title of this section resonates with Yogi Berra's enigmatic advice, because at this point in my life I had no idea where I was heading or what I really wanted to do. There was music; but my father had suggested that I would not be able to make a living from music. I didn't dare to ask him to clarify the thinking behind his advice. Maybe I would just drift along.

Thus, my pathway to a career in chemistry represented the confluence of several coincidences, and much luck – good and bad.

My 5 years at Excelsior School and Clarendon College, were expensive for my father since I was always boarding somewhere. There was neither the custom, nor the possibility, to work during vacations, as happens in North America. My father's coffers were badly depleted, as would also have been true for most middle class families. It was therefore customary for high school graduates to work for a few years, to establish some sort of financial foundation, particularly for those who aspired to further education.

As in most of the colonies of The British Empire, a job in the civil service, serving Her Majesty's Government, had status appeal. Civil servants had to dress well, shirt and tie for men, and it was considered totally uncool to wear the same outfit every day, as the English expatriates did. But the wages were paltry, and it was rumored that they could either dress "sharp" or eat, but not both.

By contrast, the thriving sugar estates were coveted destinations for young men. Not only did they pay excellent salaries, but employees were able to drive around in Estate jeeps. And more importantly, the Estates all maintained excellent, highly competitive cricket and football teams. The estate club houses, awash in subsidized rum, were alluring value-added perquisites.

But I hated cricket, and was a very feckless footballer. So I definitely lacked value-added appeal. Actually, I never had a chance to apply because of an unexpected fork in the road.

I had finished writing my Cambridge Higher School exams in early December 1951, and was at home awaiting the Christmas season, while I leisurely contemplated my future. I received a telegram (we had no telephone) from Mr. Stuart, the principal of Clarendon College saying that he wanted to see me. Although I had left school, I was terrified. What had I done now, I worried?

Far from being in trouble, he was inviting me to return to Clarendon College, 2 weeks later, as a teacher! I was stunned. I was not one of his favorite students, for that status was reserved for students who excelled at Mathematics and/or Latin. Geometry was okay with me, but not algebra and (ugh) trigonometry. And as far as Latin was concerned, I had still not recovered from Mr. Echeverier's classes at Excelsior 5 years earlier.

Mr. Stuart (or Pops, as he was known) espoused these subjects as criteria of intelligence, probably because they had factored so strongly in his own history. He belonged to a cohort of legendary teachers who, being brilliant but too poor (and/or too black) to attend the few high schools of their childhood, had climbed the ladder of Primary School – Pupil Teachers Program – Mico Teachers College. Because of their drive and excellence, they soon became Principals of Primary schools early in their careers. While on that full time job, they had engaged in correspondence courses from the University of London and earned External B. A. degrees.

Mathematics and Latin were two of the subjects Stuart had taken.

I have often marveled at the ambition, fortitude and discipline that it must have taken for this accomplishment. How could they have managed without access to libraries, tutors, tutorials, Cliff's Notes etc.?

In the small colonial island of Jamaica, news of these scholastic achievements was widely disseminated, because they provided irrefutable evidence for the ethos of upward mobility through education. Some of the achievers became prominent Ministers of Government. Others switched from Primary Schools to elite Secondary Schools, to which poverty or race had blocked their access as students, a generation earlier.

Mr. Stuart had left the über-elite Munroe College to take charge of a fledgling and floundering Clarendon College, 2 years before I arrived on the scene.

My father was of course delighted with the news of Stuart's offer to me. To him, teaching was a noble profession, and I would be the third of his children to follow in his and my mother's footsteps.

And so, in January 1952, I became a teacher at Clarendon College. I was 17 years old, and younger than many of "my students", some of whom had been my buddies and companions 4 weeks earlier.

What did I teach? I taught what I was asked (or more precisely told) to. Mr. Stuart was ahead of his time in thinking, erroneously, that any teacher worth his salt, would be able to teach any subject assigned to him. So in my time there, I taught Spanish to Cambridge Higher School candidates, even though I had taken the subject at the lower Cambridge School Certificate level – and had failed it!

Given the credentials on my Higher School's Certificate, biology would have been a logical subject for me to teach. But I was low on the biology-teacher totem pole. My zoology teacher, having finally passed the exam, was senior to me, and the Rev. Mr. Fountain was still there teaching botany with his leg propped up on a chair.

Nevertheless, in one of those strange events of fate, the teaching of biology ultimately led me to chemistry, albeit in a round about way.

I had already been a student at Clarendon College for 2 years when a new secondary school, Knox College, opened its doors only 3 miles from our house. Under the auspices of Scotland's Presbyterian Church, and the charismatic leadership of the Rev. Mr. Lewis Davidson, the school grew rapidly and gained a well-deserved reputation for incorporating several innovations, that added spark to the conventional starchy secondary schools' curriculum.

A member of the Board of Governors of Knox was the Rev. Alfred Henry, the minister of the local Presbyterian Church where my father had been organist and choir master for decades, and where I frequently played during my vacations from school. Mr. Henry was therefore a good friend of the family.

His son, David, aspired to go to medical school; but his biology was not too good. I was therefore engaged to give him private lessons during the summer vacation.

I must have done a good job, because Mr. Henry broached an idea to me. How was I doing as a teacher at Clarendon College, he enquired. Was I aware that Knox College had been sending its young teachers away for university training? No, I was not. Why didn't I transfer from Clarendon College to Knox in order to avail myself of this program, he asked. Why not, I thought.

And so I told my headmaster, Mr. Stuart, of the advances that had been made to me, and wondered whether Clarendon College had any such programs in mind for its teachers.

"What subject would you study," he asked, quite reasonably. I had not given much thought to the matter, but by reflex, I suggested geography, since it was one of my Cambridge Higher Schools subjects, and Clarendon College still did not have a "qualified" teacher in this discipline. "Oh, we can get geography teachers a dime a dozen", he said dismissively. "If you were going to study physics or chemistry, then that would be worthy of consideration."

With the Clarendon College door now apparently closed to me, Rev. Henry and Knox College became increasingly attractive. But then, one of my life's pivotal events occurred, although it would be 2 years before I was to fully appreciate it.

2.3.2 "Good Fren Betta Dan Pocket Money" Jamaican Proverb

2.3.2.1 Stan

After I had been teaching for 2 years, Stanley Shepherd arrived at Clarendon College, as the school's first qualified science teacher. As a teenager, Stan had left the exotic tourist town Port Antonio, to enlist in the British Royal Air Force. After boot-camp in Canada, he was shipped over to England just as World War II came to an end. So he never saw action. Nevertheless, he took advantage of the educational training offered to veterans. He enrolled at Exeter College (now Exeter University). And so he arrived at Clarendon College armed with a British Teacher's Certificate and a Bachelor of Science degree from the University of London in chemistry, physics and mathematics. He and I were soon to become mentor and mentee, and eventually best friends.

Physics was his first love and mathematics his second. "Chemistry is just like cooking," he said derisively – in spite of the fact that he was an excellent cook. I eagerly helped him to set up the science labs, and thereby became exposed to smatterings of physics and chemistry. I understood the latter, but not the former. And that situation persists today. If I understand it, it is chemistry; if I don't, it is physics.

The chemistry so intrigued me that I resolved to learn more. The self-help books "Teach Yourself 'This or That' " published by the Penguin Press Ltd., London, were familiar to me. So I went to the island's only bookstore, Sangster's, and purchased the 240 page book entitled, *"Teach Yourself Chemistry, A practical book of self-instruction in Chemistry, based on the work by James Knight, M.A. B.Sc., completely revised and enlarged by G. Bruce Macalpine, B.Sc."* After gobbling it up, I went on to purchase the more imposing book *A Text-book of Inorganic Chemistry* by J.R. Partington, M. B. E., D.Sc.

These books made it clear to me that chemistry was "definitely in my future." I applied myself assiduously, pottering around the lab during the evenings, weekends – indeed whenever time allowed.

Of course, nothing escaped Mr. Stuart's purview, and I was soon summoned.

"Who gave you permission to do experiments in the lab?"

"Mr. Shepherd", I replied.

"Mr. Shepherd can't give you permission, because there are fees to be paid"

And so lab fees, (an arbitrary amount, for Stan was so annoyed that he refused to give an estimate), were extracted from my monthly salary thereafter.

Interestingly, teaching chemistry to the lower grades was soon added to my assignments – but the lab fees were never rescinded.

Since one of his recommended subjects, chemistry, was clearly in my future, I revisited the issue of the school sending me to university with Mr. Stuart. But apparently I was too late!

First the School's Board of Governors, which we all knew relied on his recommendation, was thinking of "sending" one of my female colleagues to the island's branch of the University College of the West Indies. She was also a product of Clarendon College, and had excelled in mathematics, which made her one of Stuart's favourites. Second, the "Board" was concerned that there was no guarantee that I would return to the school, after university. I wondered what guarantee the female teacher had given, that I could not have provided.

Nevertheless, this would prove to be fortunate, in retrospect, because my future options would not be constrained by any contract that I would have been obliged to fulfill.

2.3.2.2 Miss Vie

The Clarendon College door to my chemistry aspirations was therefore closed; but another door would soon unexpectedly open.

The key to that door was held by Mrs. Evadne Jackson, known simply as Miss Vie. She and her husband were prominent merchants in Chapelton, the village where the school was located. She was in many respects an *in loco parentis* mother to many of my school mates. All of her five children had attended Clarendon College. I was at school with some, and was a teacher of the others.

One of her sons was my classmate, and he had long since gone off to study medicine in Switzerland. Whenever I walked past her store, she would call me in to give me updates about his progress. However, on this occasion, the discussion would take a different turn. She focused the searchlight on me. "What about your future?" she demanded. "Aren't you planning to go to a university and to get qualified?" "Don't you have any ambition?" she abraded.

I explained to her that as merchants, she and her husband could afford to send their kids to university; but my father was a widowed, retired teacher living on a pension and he certainly could not help me.

"Well, how much money do you have in the bank?" she demanded.

"Bank!" I exclaimed.

"Well, how much do you pay for rent?"

"I don't pay rent. The school provides me with lodging."

"How much do you pay for meals?"

"The school also provides my meals."

"Wha' yuh a sey bwoy? " she thundered in the Jamaican vernacular. "Yuh nah pay nutten fe rent, yuh nah pay nutten fe food, an' yuh nuh hav no money in de bank!!?"

After admonishing me about several things, imagined and real, that I should not be spending my money on, she instructed me as follows:

“Now, yuh bring me yuh pay at the en’ of every mont’.”

At nearly 21 years of age, I had been working for 4 years, but I dared not disobey her. So, at the end of every month, I would take my paycheck to her and she would discuss my debts, telling me which to pay, and which to forget about for the time being. I was getting my first lessons in how to construct a budget. She would then give me “pocket money” and deposit the rest in the Government Bank run by the local Post Office.

So when the Clarendon College “Board” closed its door to me, I found to my great surprise that, thanks to that wonderful Miss Vie, there was nearly enough money in my Post Office bank account to purchase a one-way ticket to Canada.

There was of course no way that I could ever repay Miss Vie for her selfless kindness and generosity. She had intervened in my life with no imaginable benefit to herself, and with nothing other than my genuine interest at heart. Nevertheless, I did make a gesture to thank her, in some small way, for her acts of love and confidence, given at a time when I needed them most desperately. At a banquet to celebrate her 90th birthday, I took the opportunity to give her my Haworth Medal, the world’s *premier*e prize in carbohydrate chemistry, that had been awarded to me in 1995 by the British Royal Society of Chemistry.

She had extracted a long standing promise from me, that regardless of where I was in the world at the time of her death, I would return to Jamaica to be an eulogist at her funeral. I fulfilled that commitment in October 2007, when she passed away at the ripe age of 100.

With my airfare out of the way, my wonderful siblings collaborated to provide one semester’s fee at a Canadian university.

Chapter 3
Canada – Very Fortunately

3.1 Queen's University – By Another Happy Default

3.1.1 Fortunately Before the Age of SAT Exams

The year was 1956 and the paroxysms of the civil rights revolutionary wars had made the United States an extremely uninviting destination for this black-skinned Jamaican. However, as members of the British Commonwealth of Nations, Canada and the islands of the British West Indies have been connected since the days of slavery. Salted cod fish was a staple source of protein in the diet of slaves. Tons of it moved southward from Halifax, Nova Scotia, on ships that returned northward with hogsheads of rum and bales of sugar.

Today, that iconic source of protein is prohibitively expensive. Nevertheless, "ackee an' sal' fish", remains the favorite breakfast delicacy in Jamaican cuisine.

In more recent, happier times, the connections to Canada have been more felicitous, and so Canadian universities have been favored destinations for West Indians. McDonald College of McGill University, and the Ontario Agricultural College, now part of the University of Guelph, produced many West Indian agriculturalists and veterinary surgeons.

So, I sent some applications to Canadian Universities. The University of Toronto was my first choice because I had good friends who were studying there. But my application arrived late, as was also the case at McGill University in Montreal. Queen's University, in Kingston, Ontario, about half way between Toronto and Montreal, was still receiving applications. But my Toronto consultants warned me that Kingston, Ontario, would be nothing like Kingston, Jamaica. Indeed, they ridiculed it as some sort of hamlet, distinguished as the location of Canada's major maximum penitentiary, an outpost for the Canadian Armed Forces garrison, as well as the uniformed, erect, in-step cadets of the Royal Military College.

That Kingston was Canada's first capital, the site of Fort Henry, entrusted with the formidable task of protecting Canada from United States aggression, was not

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_3,

mentioned. They recommended that I go to Queen's for the first year and then transfer to Toronto.

It proved to be my good luck that Queen's was the only door that was open to me in 1956. The smallness of the university, its campus nestled on the picturesque banks of Lake Ontario, ensured that all people and all things were within easy reach. The hostility of the native Kingstonians to rowdy, invading students, the muscle of the soldiers, and the starchiness of the Royal Military Cadets was palpable. So friendships within the University community were facilitated. I met my wife there, and the Queen's bug was so infectious, that our children headed north from our home in North Carolina to Queen's, where they linked up with cousins and children of their parents' college mates.

Thankfully, 1956 was the pre-SAT age; but I was armed with the required letter of recommendation from Mr. Stuart, the headmaster of my High School, Clarendon College, and subsequently my boss when he invited me back as a teacher. The letter of recommendation stated that I "was never more than 'average' at general intellectual activities", but that I possessed "a high degree of interest and ability in aesthetic subjects, particularly Music". This candor, while accurate, might have been more appropriate if I was planning to enroll in a Conservatory.

But I was aiming for chemistry, and Dean Earl was clearly puzzled because he noted that there was no chemistry on my high school's transcript. However, since at the age of 22, I could be considered a mature student (indeed, I was older than my faculty advisor), he would give me conditional acceptance; but he emphasized that he would be watching me.

Before leaving the Dean's office, I had the gall to press my luck further. I pointed out that I had done very well in botany, zoology, economics and geography at the Cambridge Higher Schools level, and so maybe he could give me some extra credits. He agreed grudgingly, but not before adding, rather severely, that I should not expect to get my degree on the basis of my Cambridge Higher Schools Certificate.

These credits placed me somewhere between freshman and sophomore levels, and armed with the knowledge gained from "Teach Yourself Chemistry" and Partington's Inorganic Chemistry, I was placed in sophomore organic and analytical chemistry courses. My first lab in the latter subject said something like "you are provided with hydrochloric acid of density 1.2. Prepare 1 L of 1.0 Normal hydrochloric acid." I turned to George Neville the student at the next station and asked "What is density?" Clearly astonished at my unfamiliarity with fundamental high school chemistry, he steadied himself before graciously answering my question.

In my second year at Queen's, roughly equivalent to my junior year, I took an upper level biology course, advertized as plant physiology. The topic did not "light my fire" but it turned out to be much more interesting than I had expected, because it was largely about the chemistry of plant life. We have all learned in primary school that plants and animals are locked in a cycle of interdependency. Plants take in carbon dioxide and use it to make the complex compounds that are found in our foods. Animals eat the plants for energy, in the course of which carbon dioxide is evolved, which is then recycled through plants.

The German-British scientist, Sir Hans Krebs, had received the Nobel Prize in 1953 for charting some of the chemical processes by which nature uses carbon dioxide as the building block for complex organic molecules. The process, known eponymously as the Krebs cycle, is evidently important for understanding the biochemistry of living organisms.

The Queen's professor for the plant physiology course was Dr. Gleb Krotkov, a Russian emigrant. His wife was the calculus tutor for Professor Jeffrey's course. The Professor's eccentricity had been certified on the day when he walked into the lecture theater and placed his garbage on the lectern, having left his briefcase at his driveway. Mrs. Krotkov was in constant demand, because the assigned textbook, authored by Professor Jeffrey, was chock full of errors. Calculus is hateful enough, without having to find out, after slaving all night on the problem, that the answer in the back of the book is wrong.

So I got to know the Krotkovs very well, and I had the good fortune to visit them at their home frequently. I recall that in making coffee, Mrs. Krotkov cracked an egg into the coffee grounds! It must be a Russian thing. They also introduced me to chocolate covered ants, served as *hors d'oeuvres*.

Professor Krotkov was interested in seeing how the Krebs cycle was obeyed by various local plants. To this end, the plants were fed with radioactive carbon dioxide, and after a period of time, they were harvested and analyzed to see how the radioactivity had been distributed among the compounds that the plant had synthesized.

Of course, the plants had to be healthy, and my initial task was to determine the optimum conditions for growing the plant of interest. I never had, and still do not have, a green thumb, and my plants looked frightfully sick. Indeed when I showed them to Professor Krotkov, he exclaimed, "I think we will throw those away."

Nevertheless, he was most conciliatory, and at the end of the semester, he gave me an "A," presumably for effort. He was impressed with my grasp of organic chemistry which I frequently showcased in class as we went through the chemical transformations of the Krebs cycle. So he invited me to do a (paid) summer internship in his lab.

By happy coincidence, or maybe a blessing, I had actually wanted to work in Kingston for the summer so that I could take extra courses and be able to graduate in the following year, after 3 years at Queen's. However, as was always the case, finances were a major concern. For my first summer in Canada, I had worked at Polysar, later Polymer Corporation, in Sarnia. This industrial job paid handsome wages, as a result of which my second year was economically painless. A university internship for my second summer would not pay nearly as well, but I had won some academic scholarships which would ease matters. However, although I did enjoy the chemistry in Professor Krotkov's plant physiology course, a future of optimizing plant growth did not appeal to me. So, I decided to look for an internship elsewhere.

3.1.2 *Professor J. K. N. Jones, FRS Comes to Queen's – My Disastrous Internship*

John Kenyon Netherton Jones (JK) had recently been raided by Queen's from Bristol University in England, to become the Chown Research Professor of Science, a position that required neither teaching nor administrative duties. His distinction was to be soon embellished by election to elite Fellowship of the Royal Society of England in 1957, added prestige accruing because he had been elected at the youthful age of 45. This remarkable event had been felicitated by way of a lecture to the entire Faculty of Science.

Naturally, attendance at this distinguished lecture was required for all chemistry majors. We were impressed by this man with the buck-teeth, who was such a red hot scientist, and yet came across as "nice guy". The lecture was certainly above our heads, but I remember how he ended the lecture. He noted that chemists were not known for their commitment to poetry, and to dispel that canard, he provided an example based on the following story.

"In a previous age, ladies tried to beautify themselves by anointing their skins with silver nitrate solution. One lady was perplexed when her skin turned black.

'We do not share her great surprise,
We know the truth that underlies
This lady's change of hue.
For what she thought was H_2O
Some H_2S contained, and so
She came down in Group Two' "

(The old method of determining metals in a sample was to dissolve them, and treat the solution with a series of reagents to see which caused a precipitate to form. Hydrogen sulfide (H_2S) was the reagent used in Group II, and if silver was present, black silver sulfide would be precipitated).

An internship under his guidance was distinctly appealing to me; and indeed it was my good fortune to spend the three summer months of 1958 in JK's lab.

But there were some blemishes. Indeed, a fellow student told me, somewhat inartfully, that according to his sources, "I had not crowned myself with glory" during my internship. Regrettably, that conclusion was justified. My experiments all seemed to go wrong. Fortunately, I did not cause any fires or explosions, but if the reported yield of a reaction was 10 g, I was lucky to get half that much. I might as well have been throwing the chemicals down the drain. The "good hands" that are the hallmark of an efficient experimental chemist, were as absent in me, as were the "green thumbs" in growing Professor Krotkov's plants.

These bad lab experiences foreshadowed a future in which my own research students (Fraser-Reid's Rowdies as they are known) would react with trepidation whenever I ventured into the lab to carry out an experiment. They quickly put some distance between themselves and my work station.

But my summer of 1958 was not all bad. In fact, it was exhilarating from a different perspective. The elective in which I enrolled was a "Reading Course" offered by the inspiring teacher, Professor Robert Moir. The textbook for the course was the ponderous monograph "Structure and Mechanism in Organic Chemistry", based on a series of lectures that had been given at Cornell University by Professor Sir Christopher Ingold of the University of London. As implied by the title, the book, 828 pages long, attempted to codify how chemical reactions occurred, by rationalizing why compound A reacted with compound B, but not with compound C, to give compound D, but not compound E.

It was tough going not only because the subject matter itself was dense, nor because of Sir Christopher's ornate writing style, but because I was also encountering many of these reactions for the first time. So I had to spend a lot of time in the library reading about these reactions, so that I would be able to appreciate the subtlety of Sir Christopher's rationalizations. This was excellent training for doing scholarly research, and in this connection, the self-study regimen of my high school years at Clarendon College again proved valuable.

The Reading Course thoroughly captivated my interest in the mechanistic aspects of chemical reactions, and provided a perfect and necessary counter to my less-than-stellar performance at the "bench" that was simultaneously underway, in JK's lab.

With the help of an excellent grade in the Reading Course, I was destined to graduate with an Honors degree in 3 years.

3.1.3 Yet Another Hurdle – Physics

But not before my high school deficiency returned and raised its ugly head once again.

I was due to write my final exams in early April 1959, and if everything went well, I would be ready for convocation in May. But in February, I was summoned by the University's stern gatekeeper, Miss Jean Royce the Registrar.

"Mr. Fraser-Reid, I have been going over your transcript and I do not see any physics. I have also gone over your high school transcripts from Jamaica and physics is also not present."

I explained to Miss Royce that physics was not taught in my high school in Jamaica, hence its absence.

"Well, I'm sorry to have to say this, but you cannot get a Bachelor of Science degree from Queen's University without having done *some* physics."

With this categorical statement, I watched as my hopes of graduating in May flew out of the window of Miss Royce's office.

But Miss Royce was really a sheep in wolf's clothing – at least when it came to West Indian students, for whom she reputedly had a soft spot. And not without reason, because in spite of the financial hardships that most of us endured, many of my predecessors had proved themselves to be outstanding achievers, leaving trails scattered with prestige awards.

And so she suggested something to me.

“Why don’t you go over to the nearby high school, Kingston Collegiate and Vocational Institute (KCVI), and ask the physics teacher, Mr. Earl (no relative to the university’s Dean Earl) if you can sit the grade 13 physics exams with his students.”

And so I made my way to KCVI to meet with Mr. Earl, who turned out to be the most concerned physics teacher imaginable.

“That would be fine with me; but how could you manage that?” he worried. “Your final exams will be finished around mid-April, and the grade 13 exams are set for the last week of April. You would only have about 2 weeks to study for it.”

Well, I did write the physics exam, and I got an A +.

Genius? No!

As part of the chemistry program, I had to take 2 years of physical chemistry, one semester of electrochemistry, and one of thermodynamics, all of which drew heavily on physics. So I borrowed the freshman Physics textbook from fellow West Indian, Barry Carr-Brown of Trinidad, and taught myself the required physics for my chemistry courses. So all I needed to do in those 2 weeks was to disentangle the chemistry from the physics.

As a result of my physics credit, I graduated on time in May, as did Barry, the owner of the textbook, which I had hoped to return to him when we meet for our 50th reunion in May 2009. Unfortunately, illness kept him away.

3.1.4 A Carbohydrate Chemist by Default

I was planning to go to Jamaica after convocation, but before doing so, I needed to sort out my future chemistry plans. I had been so stimulated by the Reading Course that I had done with Professor Moir that his Research Group seemed like a logical fit for me. His lectures were intense and demanding – which was fine with me.

Professor Moir was a graduate of Queen’s, and was a phenomenon in his time there, having obtained his bachelor’s degree while in this teens. His expertise covered a broad palette, and rumor had it that he lectured to engineers in advanced calculus, and to English majors on Shakespeare!

In addition to being an excellent teacher, he had shown himself to be an affable, empathetic mentor. He later told me that sophomore girls, devastated by break-ups with their freshman-year boy-friends, flocked to his office for comfort. He reputedly told them that “the young man is obviously a jerk, and doesn’t deserve a nice girl like you”. Luckily he was still dispensing such consolation, when my daughter, Andrea, a Queen’s chemistry major a generation later, sought his help with her sophomore blues.

And so I felt comfortable approaching him about my future in Chemistry.

“Professor Moir, I would like to join your Research Group next fall”. Without a moment’s hesitation he declined! “I think you should go and see Professor Jones”

Oh no! Why? After all I got an A + in his course. Was it because I had interned with Jones the previous summer? Was it because “I had not crowned myself with glory" during that internship? Whatever the reason, going to see Jones was not something I looked forward to.

But one has to be brave.

"Professor Jones, can I join your Research Group next September as a graduate student?" I asked, as the specter of my less than glorious internship hung in the air.

In keeping with his "nice guy" reputation, Professor Jones restrained himself from saying to me "Bert, take a hike." Instead, he couched his lament with classy eloquence.

"The problem Bert is that I only have 2 vacant spaces and I want to keep them in case students with first class honors degrees show up."

"But sir, I just graduated with first class honors", I eagerly advised him.

"You did!" he exclaimed with undisguised incredulity.

"Yes sir, and I also came second in my graduating class, as a result of which I have a full university scholarship to pursue a Master's degree."

The poor man was caught between a rock and a hard place.

"I guess I will have to take you then," he said somewhat ruefully.

With my admission to JK's group now secure, I was free to spend the summer months of 1959 in Jamaica. It was to be my first visit since I left in September 1956. My father had passed away in 1957, but there was no question of me coming out for the funeral, because air travel was well beyond my financial resources.

3.1.5 Graduate School – Curiosity and Serendipity

When I entered grad school, a high school friend with a strong entrepreneurial bent approached me with a proposition. I should discover a reaction that could be used to make a new product, drug, snack, medication – whatever, and he would handle the marketing issues. We would both get rich.

J. K. N. Jones' lab was not the place to explore such enthusiasms. Curiosity was his stock in trade. Why not mix this with that and see what happens? – or so it seemed to me. A chemical reaction that went well was great; but one that did NOT was better.

A case in point was my assigned project, which was to carry out a seemingly well-understood series of procedures. But something weird happened. In view of the crises during my internship, I wondered whether this "weird happening" was yet another occasion where I was to "not crown myself in glory".

But no! JK was enthused by the "weird happening" and from that experience, I took the early lesson that a "weird happening" is Nature's teachable moment and therefore worth pursuing even if it meant that we had to jettison the original plan – which we did!

And so, my first publication emerged from just such a serendipitous event: "The Demethylation of Sugars with Hydrogen Peroxide" by B. Fraser-Reid, J.K.N. Jones and M. B. Perry, *Canadian Journal of Chemistry* volume 39, (1961) 555–563.

Jones' lab was a hive of diverse activities, some of which were well ahead of his time, as I was to appreciate some 40 years later, when a young colleague expressed admiration, upon learning that I had done my Master's degree under Jones' supervision.

For example, Nature uses enzymes to carry out chemical reactions, some of which are "destructive", for example, breaking down sugar inside our bodies to provide energy, while others are "constructive", for example, converting carbon dioxide into complex compounds to obtain the food of plants. Chemists have always been humbled by Nature's efficient use of enzymes, and they have tried to decipher the secret recipes. JK was no exception.

Today many of these enzymes are available from supply houses; but in 1959 there was no such luxury. The enzymes had to be extracted from wherever Nature put them. Thus, some of Jones' students would be dispatched to Kingston's abattoir to return with buckets of cow's blood. Others would go to the hospitals to collect umbilical cords. Some would be sent 150 miles away to Connaught Laboratories in Toronto (where insulin had been discovered) to obtain human blood. (I wonder what they would have said if the Royal Canadian Mounted Police stopped the car and discovered their cargo.) The desired enzymes would then be extracted by, what seemed to be ghoulish, punishing, precise, and smelly procedures. Those young scientists surely had patience and "good hands".

3.1.6 Sugar → Splenda Begins Elsewhere in the Lab – By Accident

However, scientists, even those as esteemed as Professor J. K. N. Jones (JK), always have to raise money to support their curiosity, and the late 1950s was no exception. But fortunately the Sugar Research Foundation emerged, and morphed into The International Sugar Research Foundation. The burgeoning excess of sugar on the world market, brought about by its ready availability from sugar beets, challenged curious chemist to come up with imaginative ways of using sugar.

Rachael Carson's book *Silent Spring,* published in 1962, posited that the pesticide DDT (**d**ichloro**d**iphenyl**t**richloroethane) had caused massive environmental damage. This triggered world-wide search for a safe successor to DDT. According to Dr. Malcolm Perry, Professor Jones' right-hand-man at the time, an impetus to install chlorines in sugars, was the possibility that such products might prove to be pesticides which would be environmentally benign. I do not know what JK's reasoning was, but I will be imaginative. Part of the problem with DDT is that it is insoluble in water. But sugar is water soluble, and so a sugar-based compound, with one or two chlorines replacing hydroxyl (i.e. OH) groups, should still be water soluble. This would enhance the chances of it being biodegraded by nature. Thus a sugar-based pesticide having these properties, would not only be eco-friendly, but would cause the worldwide surplus of sugar to vanish.

Another (possible) impetus, human rather than scientific, may have come from the intellectual rivalry between English and German schools of carbohydrate chemistry. Jones had been a product of the English School of carbohydrate chemistry that had flourished under the martinet leadership of Professor Sir Walter Norman Haworth, winner of the Nobel Prize in Chemistry for his work on Vitamin C (nicknamed by his perplexed students as "godnose").

The German School, older and certainly more eminent, had developed under Emil Fisher, properly regarded as the Father of Carbohydrate Chemistry worldwide. He had received one of the earliest Nobel Prizes in chemistry for, among other things, determining the structure of glucose.

There was a healthy rivalry between the English and German schools over many aspects of carbohydrate chemistry, and it would certainly not be surprising if gamesmanship sometimes intruded.

Sulfuryl chloride is a well-known chlorinating agent. It is not a nice substance. It is highly toxic and corrosive, and may be carcinogenic. When the container is uncapped, a dense choking, tearing, searing fog emerges, which is soon converted to sulfuric and hydrochloric acids. One wonders just what Professor Burckhardt Helferich, a German chemist, had hoped to obtain when he treated several sugars with this miserable reagent in 1921. That he did not get a "burnt offering" was probably cause for rejoicing. Actually, he got a respectable yield of a compound that had incorporated chlorine; but he was unable to assign its structure.

Jones and his colleagues of the English school would certainly have known of Helferich's experiment, and of his failure to assign structure. However, this "failure" should not be construed as an indictment against Helferich, because the tools available to him for structural investigations in 1921 were simply inadequate. JK's involvement, 30 years later, benefitted from new techniques for structure elucidation. One of the most powerful of these originated with the French chemist, Malaprade, and the potential of the Malaprade reaction, or periodate oxidation, was seized upon by the English school, for determining structures of carbohydrate derivatives. Jones was a prime mover in this development, and the new science would now be brought into play at Queen's (Fig. 3.1).

The lead investigator was Phil Bragg, who had obtained his Ph.D. at Bristol University under the guidance of Dr. Leslie Hough, JK's first Ph.D. student. Phil was spending a year with JK, his chemistry "grandfather" or *grossvater*, to use the German appellation.

Phil's work was in progress during my undergraduate internship in the summer of 1958, but all I knew was that when he treated methyl glucoside with the chlorinating agent, he obtained a "complex mixture." My response to this news was probably "so what else is new?" For, from my lowly, undergraduate perspective, all the reactions in the lab, including my own, gave "complex mixtures".

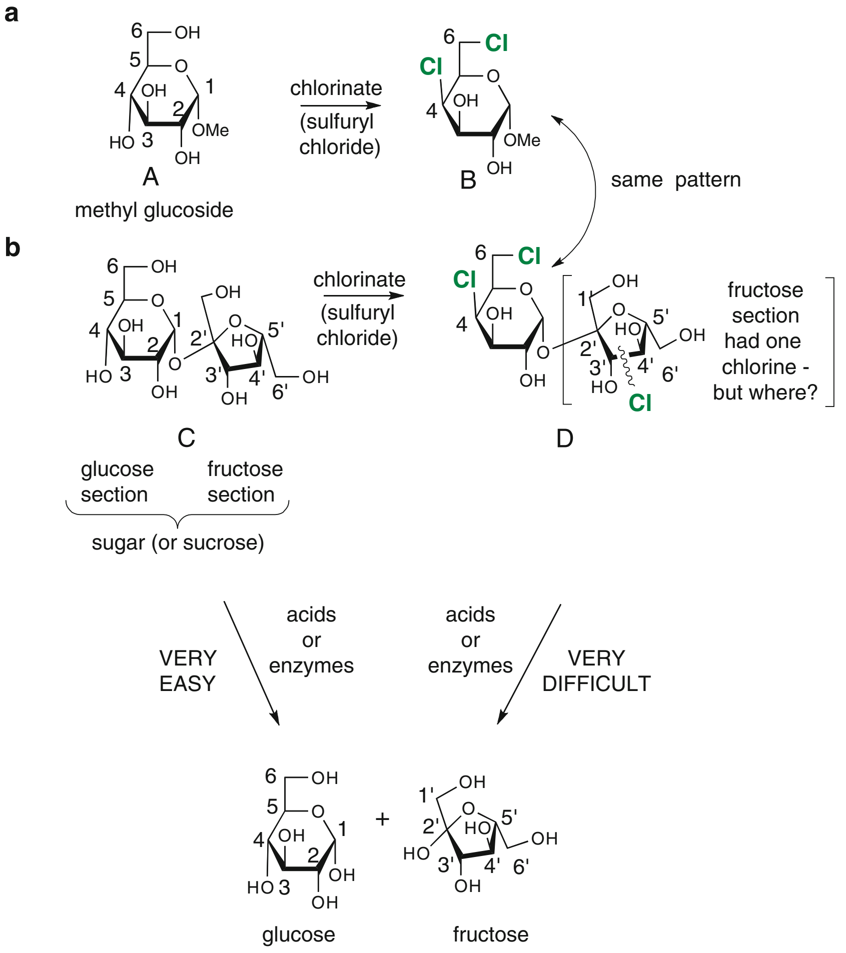
But an organic chemist who has "good hands," as Phil did (and I did/do not) will fish out the components of a complex mixture. So by the time I rejoined JK's group as a graduate student a year later, Phil had isolated the major component of the complex mixture. And his next task was to prove its structure.

Fig. 3.1 Professors Raymond Lemieux, Leslie Hough and J.K.N. Jones find time for some golf during the 1967 Symposium sponsored by the International Sugar Refiners Association, held at Queen's University, Kingston, Ontario, Canada. Professor Jones died in 1977 at age 65, and Professor Lemieux died in 2000, at age 80. Professor Hough continues to enjoy great health at his home in Wimbledon, London, UK. (The author thanks Professor Hough for the photograph)

Today, determining the component's structure would be accomplished in a matter of minutes by the use of Nuclear Magnetic Resonance (NMR) spectrometry, which was then in its infancy, the ground-breaking experiments having been described in 1958 by Canadian chemist (and my future Ph.D. mentor) Raymond Lemieux, then at the University of Ottawa, along with physicists at Canada's National Research Council. But Queen's did not have an NMR spectrometer, and so Phil used the Malaprade (i.e. periodate) oxidation which detects OH-groups on adjacent carbons.

(Nuclear Magnetic Resonance is the science behind MRI [Magnetic Resonance Imaging] that is so widely used in medical diagnosis. The word "nuclear" was apparently dropped lest worrisome patients envisage a mushroom cloud).

Scheme 3.1a shows a simplified version of Phil's experiment on methyl glucoside. The glucose skeleton is represented here as a hexagon rather than linearly as in Scheme 2.1, but the numbering of the carbons is the same. Note that the hydroxyl (OH) group at position 6 is "off" the hexagon, while those at positions 2, 3 and 4 are directly attached. By clever use of Malaprade oxidation, Phil deduced that the OH groups at positions 4 and 6 had been replace by chlorine.



*primed numbers are used for the fructose "pentagon" to differentiate from the glucose "hexagon"

Scheme 3.1 Jones' 1958 chlorination of methyl glucoside and sucrose

Phil also determined that the chlorine at position 4 entered from the "up" side of the hexagon – or in Chemistry-speak, the orientation at position 4 had been inverted. This would turn out to be highly significant.

In light of the success with methyl glucoside, (Scheme 3.1a), and the availability of funding from the Sugar Research Foundation, it was logical for JK to "see what would happen" with sucrose (Scheme 3.1b) which, as evident from Scheme 3.1, shares some structural features with methyl glucoside,

Accordingly, Phil Bragg chlorinated sucrose and obtained a product which had several chlorines in it. Scheme 3.1a, b show the similarities of the hexagon rings in methyl glucoside, and sucrose. It was therefore possible to establish that two chlorines would be introduced at positions-4’ and -6’ of the glucose hexagon.

In the course of the latter experiments, Phil and JK made an observation which, in retrospect, foretold one of the salient properties of sucralose. They found that whereas sucrose, **C**, is rapidly cleaved into glucose and fructose by treatment with acids or enzymes, the chlorinated product was so robust that “the vigorous conditions of hydrolysis necessary to cleave the interglycosidic linkage destroyed the fructose moiety. . .” Thus, Phil and JK had obtained evidence that the chlorine(s) located in the pentagon (fructose) inhibited cleavage.

This passing observation was a poignant portent regarding the non-caloric properties of sucralose, as will be discussed in Chap. 5. In the body, ready cleavage of the interglycosidic linkage of sucrose releases glucose and fructose which are excellent sources of calories. *Jones’ chance observation meant that chlorine(s) in the five membered ring inhibited cleavage, and thus the release of caloric fragments.*

(For further comment on the chemistry shown in Scheme 3.1, please see Appendix A)

3.1.7 Crossing the Atlantic Ocean

Phil Bragg’s exploratory reactions were successful in the sense that interesting new products had been obtained. However, the percentage yields were poor and it was necessary to try and improve this aspect, or at least understand exactly what was going on in the reaction.

That task fell to Harold Jennings, a cockney Londoner who, with me and my undergraduate class mate Solomon Gunner, joined JK’s group as Masters’ candidates in the fall of 1959. The original project assigned to Jennings was not going very well, and after some frustrating months, he suggested to JK that he resurrect the chlorination project which had been abandoned after Phil returned to England.

In a string of publications between 1962 and 1966, Jennings reported experimental procedures that improved the yield of the chlorinated products obtained and clarified the mechanisms by which the chlorines were inserted into the sugar skeleton. These achievements were catalogued in his Ph.D. thesis.

It is customary for freshly minted Ph.Ds. to spend a year or two working with a different professor for further training. For example, Phil Bragg, who initiated the chlorination studies in Jones’ lab, had obtained his Ph.D. with Leslie Hough at the University of Bristol. Recall that Hough was Jones’ first Ph.D. student at the University of Manchester and had moved with him to the University of Bristol. After Jones moved to Queen’s, Hough remained at Bristol. Harry Jennings would now return to his native England to join Hough’s lab as a post doctoral fellow.

This dance of scientists between Ph.D. *vater* and Ph.D. *grossvater* may sound incestuous; but it was not unusual in the carbohydrate community of that day.

Chapter 4
London – Hough, Khan and Pfadnis Get Together

4.1 Familiarity Bred Excitement

It cannot be over-emphasized that the experiments that were being done in Professor Jones' lab at Queen's University in Canada, were totally unrelated to Splenda, because Splenda and sucralose, its sweet ingredient, were not known at the time. The experiments were not target-oriented in any way – if one excludes the wistful premise that a pesticide would result from these excursions. Such a hope-for–the-best project is extolled as involving "pure" research, which is not to say that it is useless, because such "pure" projects are frequently the lodestones of new discoveries in the hands of enterprising scientists.

The work in the labs of Professor Leslie Hough was a case in point. This should not be surprising, because Hough was Jones' first Ph.D. student at the University of Manchester, and moved with him to the University of Bristol, remaining there after Jones left for Canada. By the time Harry Jennings returned to England with his freshly minted Ph.D., Hough had moved from the University of Bristol to become Head of the Chemistry Department of Queen Elizabeth (later King's) College, a campus of the University of London located in the southern part of London.

With Jennings joining Hough's group, chlorination of sugars, that had been extensively studied in J. K. N. Jones' lab at Queen's University, Canada, had now been taken across the Atlantic, by one of my M.Sc. classmates, to the labs of Leslie Hough, Jones' first Ph.D. student, where sucralose would be discovered within a decade.

However, I must repeat that no one could have foreseen what the decade ahead held in store. And most significantly, in Hough's lab, Jennings did NOT work on the project that, fortuitously, led to sucralose. Notably, Hough and his colleagues were interested in using sucrose to explore approaches to new antibiotics – as will be discussed more fully in Chap. 6.

Some years earlier Dr. Riaz Khan had obtained his Ph.D. under Professor Hough's supervision as the recipient of a **Sugar Research Foundation Fellowship**. He had then pursued advanced studies at citadels of carbohydrate chemistry in

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_4,

Norway and Canada before accepting an invitation from Tate & Lyle to return to London. The Company had established a Center to explore chemical modifications of sucrose, that could be used to decrease the growing surplus of this once treasured commodity. The head of the Research Center was the late Dr. Chuck Vlitos who appreciated the concept of "pure" research, and funded it accordingly. By providential circumstance, the Center was housed, not on Tate & Lyle's premises, but in rented space at the University of Reading, a hop and a skip away from Queen Elizabeth College. This proximity facilitated intense collaboration between the research groups of Hough and Khan on the chemistry of sucrose.

The collaboration led to over 20 papers published between 1970 and 1975 in a series appropriately entitled "Sucrochemistry Part I, II, III, etc—." The concept of *Sucrochemistry* had been advanced in the 1950s by H. B. Haas, director of the Sugar Research Foundation in New York. He said that sucrochemistry describes "the Branch of Science and Technology whose objective is to bring added markets to sucrose and its byproducts by chemical utilization." The Sugar Research Foundation must have been ecstatic to see that its funds were being used with such a high productivity quotient.

4.2 Khan's Group Made Sucralose—Before It Was Known

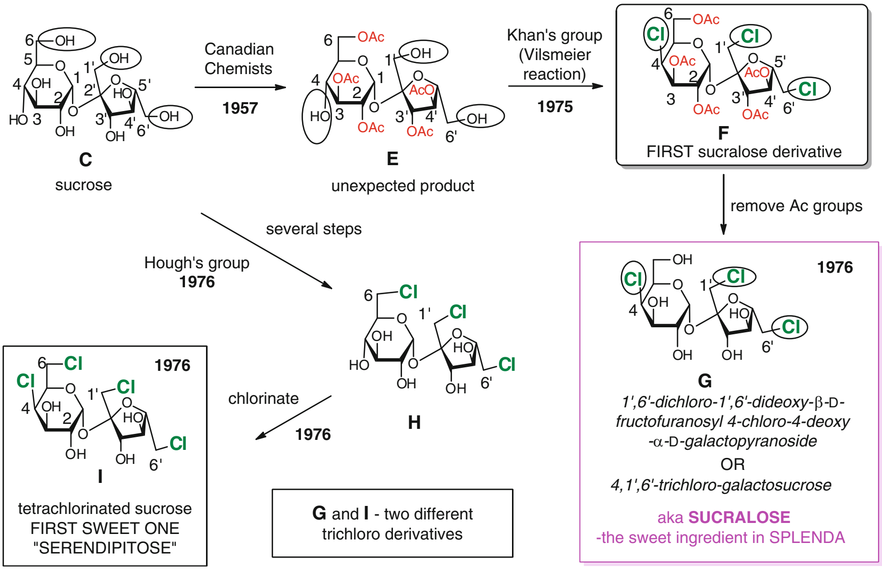
The first preparation of sucralose was, to put it mildly, uneventful. For one thing, the technical name, *1',6'-dichloro-1',6'-dideoxy-β-*D*-fructofuranosyl 4-chloro-4-deoxy-α-*D*-galactopyranoside*, was a mouthful even for a carbohydrate chemist.

Not surprisingly it went unnoticed?

In discussing Scheme 4.1, we must first examine the diagram of sucrose (structure **C**). It will be seen that there are eight hydroxyl (OH) groups; but it is obvious from the work of Jones and Bragg in Scheme 3.1b, that only a few of them were replaced with chlorine. This indicated that they have different reactivities. Hough's first 15 papers, *Sucrochemistry Part I to Part XV*, tried to rationalize these different reactivities.

However, in Scheme 4.1 we encircle three-OH groups of sucrose, **C**, that are NOT directly attached to the rings. These are said to be "primary"; the others are "secondary". Primary-OHs are more accessible. However evidence *seemingly* to the contrary, had been encountered in 1957 by Canadian scientists in Hayward's lab at the University of British Columbia, who obtained compound **E** in which one of the free hydroxyls was at the secondary position-4. (A rationalization for this apparent phenomenon is given in Appendix **B**, Scheme B1).

Fifteen years after the above Canadian report, Khan's group at Tate & Lyle (Reading) applied the Vilsmeier chlorination reaction (which will be discussed in Scheme 7.4) to compound **E.** They obtained the trichlorinated derivative **F**, **which was, in reality, the acetylated version of what was to become known as sucralose.** A year later, deacetylation removed the five **red Ac** protecting groups thereby affording compound **G.**



Scheme 4.1 The uncelebrated synthesis of sucralose and "Serendipitose"

This compound, G, is in fact today's sucralose; but Khan's paper made no fanfare or drum roll to announce its discovery – *because its sweetness had not yet been discovered!*

Subsequently, chlorination of H gave I with four chlorines – which led to the EUREKA moment.

(For further comment on the chemistry shown in Scheme 4.1, please see Appendix B)

4.3 Hough's Group Made "Serendipitose"

Obviously, from the above, selective chlorination at all primary positions of sucrose, **C**, was still a requirement, and subsequently, a lengthy sequence by Hough's co-workers achieved the desired structure, compound **H** (Scheme 4.1). Notably, both compounds **G** and **H** have three chlorines, but in different positions. (For a comparison of their sweetnesses see Table 5.1 below).

Addition of a FOURTH chlorine as in **H**, would mean that 50% of the OH groups of sucrose had now been replaced. Such a molecule would invite wide speculation about its properties such as solubility in water, solubility in chloroform, melting point, optical rotation – etc. But none of these would include the property that Pfadnis would soon discover.

4.4 EUREKA—Shashikant Phadnis Finds That Serendipitose is Sweet!

Wikipedia reports that "[on] a late summer day, Phadnis was told to test the powder. Phadnis thought that Hough asked him to taste it – so he did."

To get the "real" truth, I have obtained written communications from Professor Leslie Hough, Dr. Riaz Khan, and Dr. Shashi Phadnis outlinng their recollections.

4.5 Recollections From the "Horses' Mouths"

Professor Hough recalls that post-doctoral student Shashi Phadnis, a native of India, had prepared the tetrachloride of sucrose, structure **I** (Scheme 4.1) in the labs at Queen Elizabeth College.

4.5.1 "Horse" #1: Dr. Shashikant Phadnis (June, 2011)

"My work at QEC *(Queen Elizabeth College)* was aimed at chemical modifications of sucrose for possible applications in the industry. As a part of it, I prepared a number of sucrose derivatives – many of them for the first time. We were particularly interested in chlorosucroses. During discussions (sometime in mid-1975), Les Hough suggested me to **test** a sample of 1',4,-6,6'-tetrachlorogalactosucrose *(structure **I**, Scheme 4.1)* which, perhaps he wanted to send to Tate & Lyle plc. I thought I needed to **taste** it ! My thinking was not unusual because we were also interested in knowing if one could enhance the natural sweetness of sucrose by **playing around with its structure. (emphasis added)**

"So, I took a small quantity of the sample on a spatula and tasted it with the tip of tongue! And what a surprise! It was intensely and pleasantly sweet. Then, I went on to taste, one by one, all sucrose derivatives that were available on my bench, and found many of them to be sweet, although intensity of their sweetness varied. *(So Dr. Phadnis had made observations about the varied sweetness of chlorinated sucroses similar to what will be seen in Chap. 5 – albeit qualitative rather than quantitative).*

"When I reported my findings to Les, he too was surprised and a bit worried. "Are you crazy or what", he asked me. "How could you taste compounds without knowing anything about their toxicity? It could be hazardous". I assured him that I tasted the compounds alright but did not swallow them.

"Subsequently, Les himself came to my laboratory and once again, we tasted those compounds rather systematically i.e. by preparing their standard solutions and diluting them to the concentrations where their sweetness matched with the sweetness of 4% aqueous solution of sucrose.

“Les then christened the aforesaid tetrachloro derivative as Serendipitose! Later on, Les even had a cup of coffee sweetened with a few particles of Serendipitose. When I reminded him that it could be toxic (as it contained high proportion of chlorine), he simply said, “Oh forget it, we’ll survive!” and gulped down his coffee.”

NOTE ADDED BY AUTHOR: As of November 28, 2011 both Professor Hough and Dr. Phadnis enjoy great health, 35 years after “the tasting”.

4.5.2 “Horse” #2: Dr. Riaz Khan (October, 2009)

Dr. Riaz Khan is a former Ph. D. student of Professor Hough, and was employed at Tate & Lyle which was funding some of Hough’s work. He was the liason between both groups. The following is Khan’s 2009 recollection of the event:

“The only thing I can add to the story is that sometime during August or September 1975 (approximately) when I was working on the stability of the glycoside linkage between glucose and fructose in the sucrose molecule against acid and hydrolytic enzymes, I needed a pure sample of the tetrachloride. My own sample had some impurity. I called Professor Hough for a pure sample and he asked me to contact Phadnis who had a sample. I called him and he inquired what I needed it for. Without going into much detail, my simple answer to him was that we wanted to “test” it for something. Both (of us) being Indians, played a fortuitous role. He misheard ‘test’ for ‘taste’. And thus the discovery was made.”

4.5.3 “Horse” #3: Professor Les Hough (March 2010)

In a 2010 letter to the author, Professor Hough writes:

“Dick (Dr A. C. Richardson) and I tried it out in a cup of coffee – No problem.

“In an article entitled *The shape of sweeteners to come* by Leslie Hough and John Emsley in the *New Scientist*, June 1986, Hough wrote: “[c]uriously, these substances might still have been waiting to be tested for sweetness had not Shashi Phadnis, a graduate researcher, misheard a telephone call requesting samples of the chlorinated sugar for testing. As the caller came from a large sugar company, it is perhaps understandable that Phadnis thought that the company had requested them for tasting and so he tried them himself”.

Hough’s first disclosure of the sweetness they had discovered, was in a lecture at a Symposium sponsored jointly by the American Chemical Society and the International Sugar Research Foundation in September 1976. He announced that:

Fig. 4.1 Professor Hough (seen left in his prime) who now lives in Wimbledon, England; Dr. Riaz Khan (*centre*) in a recent photograph. Riaz now lives in England and Italy in semi-retirement, but keeps busy working with Protus Research Institute, Trieste. Riaz obtained his Ph. D. under Professor Hough's supervision, and subsequently joined Tate & Lyle's research team. Dr. Shashikant Phadnis (*right*) currently lives in semi-retirement in Pune India. Had he not misunderstood "test" for "taste", the sweetness of chlorinated sugars might never have been discovered. That one Indian could have mistaken the accent of a fellow Indian, is the basis of a modern-day legend (see chapter 4.1.5), and it underscores the role of "luck" in scientific discoveries.

*"An objective in our chemical studies on sucrose has been to enhance its natural sweetness, and we have been considerably encouraged in this direction by the surprising discovery that this…… [tetrachloro sucrose derivative **I**]….. is intensely sweet, comparable to saccharin, but with a pleasant after taste."*

It must be emphasized that the above lecture was given **2 years after compound (G), the future sucralose**, had been prepared by Khan, albeit then known by the technical name shown in Scheme 4.1.

Hough's second disclosure was in a publication 1 month later in the October 28, issue of *Nature*, a journal that prides itself in accepting only those papers which have monumental scientific significance. He began with this theme:

*"There is considerable interest in the relationship between chemical structure…..and the sweet response…..We have now been greatly encouraged by the surprising discovery that….[.the tetrachloro sucrose **I** (Scheme 4.1)]….. is intensely sweet, comparable to saccharin but without an unpleasant after-taste"*.

Hough and Khan were, of course, well aware of the potential of Phadnis' discovery, and so earlier interests in sucrose-based pesticides and antibiotics were demoted.

The disclosures were, of course, protected by a patent (1,542,168) entitled "CHLORODERIVATIVES OF SUCROSE" (Application No: 860/77, Filed 8 Jan. 1976). **Notably, this filing took place 2 years and 3 months AFTER sucralose had been unwittingly synthesized— see structure G (Scheme 4.1).** The inventors were Riaz Ahmed Khan, Leslie Hough, and Shashikant Purushottam

Phadnis, and notably, the applicant organization was not Tate & Lyle, but The Research Corporation of New York, a non-profit organization. However in the 1976 lecture to the American Chemical Society, and in the paper to *Nature*, acknowledgement was given to Tate & Lyle, as well as the International Sugar Research Foundation.

From a 2006 New Yorker article by Burkhard Bilger

"On that late summer day in 1975, Phadnis —used a small spatula—to put a little on the tip of his tongue. It was sweet –achingly sweet. 'When I reported my findings to Les, he asked if I was crazy', Phadnis remembers. 'How could —you taste compounds without knowing anything about their toxicity?" Before long, though, Hough was so delighted with the substance that he —tried putting some in his coffee.

"Oh, forget it" he said, when Phadnis reminded him that it might be toxic. 'We'll survive' "

The author is fascinated by the subtle differences in the recollections of the three participants as outlined in Sects. 5.3.1, 5.3.2, and 5.3.3. Unfortunately, who recalled what and why, is beyond the author's expertise.

4.6 A 2011 Retrospective by Professor Leslie Hough

"I thought I would explain that in September 1975 I was worried that Phadnis' ISRF [International Sugar Research Foundation] grant might not be renewed on October 1. Naturally, I wanted him to continue. He had just made a tetrachlorinated derivative of sucrose on the ISRF grant. Consequently, I was worried. I rang Chuck Vlitos, Director of Research at Tate & Lyle, Reading, and asked him if he would support Phadnis with a post-doc grant. He agreed immediately. So I switched Phadnis to a Tate & Lyle grant from October 1, 1975.

"Then the sweetness was discovered by Phadnis after Riaz rang us to request a sample of the 'tetrachloride'.

"Dilema for me then was disclosure. The next day I went to Reading and informed Chuch Vlitos. The next week there was a sugar meeting in Paris at which the Director of Research of the ISRF was present. So then, I went to Paris to inform him of the situation. Lawyers then went to and fro, and a patent for the 'tetrachloride' went to ISRF and sweetness to Tate & Lyle.

"When the tremendous cost of safety biological testing became a burden to Tate & Lyle, Chuck Vlitos engaged Johnson and Johnson to become a partner."

Would post-doctoral student Phadnis now be required to test (taste?) every chlorinated sucrose derivative that he had made?

If this were a novel, I would be free to write that he was indeed asked to do so, and that he found that the previously prepared trichloride **G** (Scheme 4.1), destined to become known as sucralose, tasted sweeter than tetrachloride **I**. In a novel, I could also manufacture evidence to show that such chlorine containing products are safe to ingest, and so there was no risk to Phadnis in his test (taste?) campaign.

But this is not a novel, and so we will reconstruct the subsequent developments, based on the published literature.

Chapter 5
Sweetness

5.1 Tate & Lyle Takes Over

5.1.1 Tested By Real Tasters – Or Tasted By Real Testers?

In a letter to the author dated March 10, 2010, Professor Hough noted that "T&L (Tate & Lyle) had screens for applications—[of our novel sucrose derivatives]—but not including sweetness, I might add".

How interesting, if not strange, that one of the world's leading sugar giants was exploring new uses for surplus sucrose that did NOT include sweetness?

However, this must have changed in a millionth of a second, because a professional Taste Panel was soon assembled. The nooks and crannies of Hough's lab were scoured for samples, and Riaz Khan's research group at Tate & Lyle's laboratory located in rented space at the University of Reading, worked tirelessly to provide additional chlorinated sucroses to be evaluated by the Panel. Professor Hough recalls that "over 100 sucrose and related derivatives" were tested.

The result was that two patents were filed **on the very same day,** January 8th, 1976, one of them (No: 1,543, 168) by Khan, Hough and Phadnis, with Research Corporation of New York as Assignee. This dealt with the preparation of chlorinated sucrose derivatives. Another, filed by Khan, Hough, Phadnis and Jenner with **Talres** Development based in Curacao, Netherlands Antilles (aka Dutch West Indies) as Assignee, dealt with the sweetness of chlorinated sucrose derivatives.

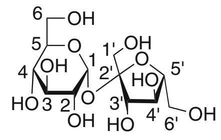
Professor Hough explains (see Sect. 4.6) that the exploratory research was funded by the International Sugar Research Foundation, while the sweetness analysis was funded by Tate & Lyle.

5.1.2 Sucralose is Identified

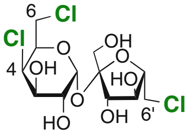
The Tate and Lyle patent evaluated the sweetness of the nine chlorinated sucrose derivatives shown in Table 5.1, the associated numerical values, (shown in blue)

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_5,

Table 5.1 Relative sweetness of some chlorinated derivatives of sucrose*. (In Appendix B we give a more detailed analysis showing the effect of adding one chlorine at a time and moving it from one position to another).



*sucrose (1)



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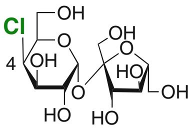

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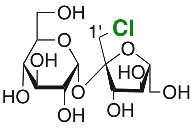

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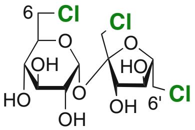

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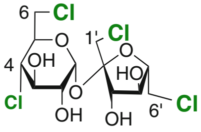

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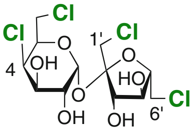

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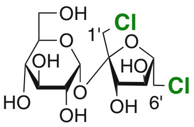
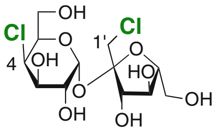


(500)



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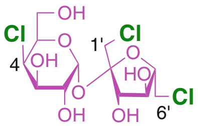


(2000) revised to 600
sucralose

*The values in blue are taken from the Table in patent #1,543, 167
(Primed numbers refer to the fructose pentagon)

being the sweetness level relevant to sucrose. These sweetness levels were determined by a professional tasting panel, whose tongues were, presumably, more sophisticated than Phadnis'.

Table 5.1 shows eight of the chlorinated sucrose derivatives that were calibrated. It is interesting to speculate about which chlorinated position confers the greatest (or least) sweetness; but this is beyond the scope of this chapter. However, a preliminary analysis is made in the Appendix B.

5.1.3 *The Amazing Human Tongue*

How amazing an instrument is the human tongue, that it can make the subtle differences seen in Table 5.1 ? One theory to account for such amazing calibration, is that the human tongue has four separate zones, rich in receptors, that enable it to distinguish between five basic tastes: bitter, salty, sweet, umami (savory), and sour (Fig. 5.1). Discrimination can therefore be very subtle as is clear by Hough's early observation, that the compound which came to be known as sucralose (Table 5.1)

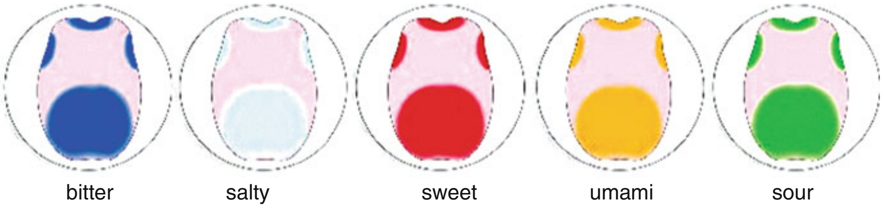
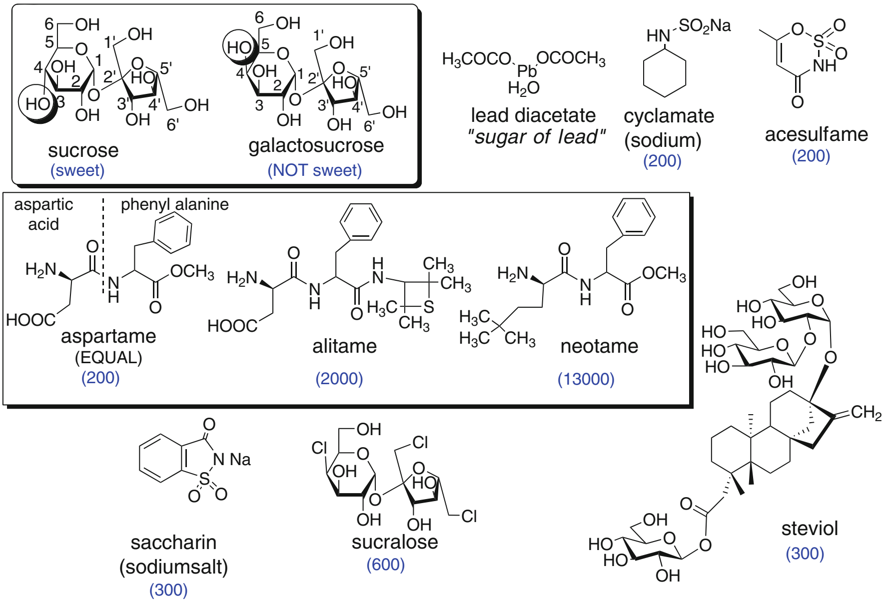


Fig. 5.1 Sensory zones of the human tongue

Table 5.2 The varied faces of sweetness. Sweetness relative to sucrose is shown in blue (Hough, 1985)



"is intensely sweet, comparable with saccharin but without an unpleasant after taste."

See also Appendix ***C*** *for more discussion of sweetness.*

5.1.4 Some Common Artificial Sweeteners: Varied and Structurally Unrelated

In light of Hough's comparison, the chemical structures of some common artificial sweeteners are assembled in Table 5.2. Also included are structures of sucrose and galactosucrose, which are different in only one aspect – whether the encircled OH at position 4 is pointing “up” or “down”. This small change causes one to be sweet, but not the other.

Sugar of Lead: The oldest artificial sweetener in Table 5.2 is lead acetate, or sugar of lead, which dates back to the Roman Empire. At that time, one stage of wine preparation involved boiling in pots that were made from lead. Wine contains several acids, one of which is acetic acid, which is also found in vinegar. The acid reacted with the lead to give lead acetate shown in Table 5.2. The compound has a sweet taste – as the author has verified. It was therefore known as “sugar of lead”, and was used as a sweetener. However, “sugar of lead” is now known to be highly toxic, a property shared with lead containing paints which were in common use, worldwide, for several decades.

Saccharin, was the first non-caloric synthetic sweetener to be popularly used. It was “discovered accidentally” in 1879 by American chemists who were experimenting with abundantly available surplus products from the coal tar industry. (Thus in common with Splenda, experiments with “surplus products” led to an artificial sweetener). Saccharin is about 300 times sweeter than sucrose, but its bitter after taste is a problem for some people (however not including the author).

Tests on rats showed that the animals developed high levels of bladder cancer, in comparison to a control population. As a result of this observation, saccharin was banned for human consumption.

However, translating the data from a rat to a human requires that the human consume 3,000 cans of diet soda per day per year – which means that the most imminent danger is that the human would burst before bladder cancer would develop.

The prohibition against saccharin was therefore lifted, and the substance is ubiquitous in the United States where beverages are served, in the pink packet known as Sweet and Low.

Cyclamate was “discovered accidentally” in 1937 by graduate student Michael Sveda at the University of Illinois, who was trying to synthesize medications for fever. An obituary in the New York Times (August 21, 1999) reports that he put his cigarette on the lab bench and when he put it back in his mouth, he detected a sweet taste. He then tasted chemicals from all the beakers in front of him and discovered the compound that he eventually refined into the sweetener. He joined DuPont after obtaining his Ph.D. The compound has faced health concerns, hence current prohibition in the United States. However cyclamates are used in other countries, including Canada.

Acesulfame commercially available as *Sweet One* was “discovered accidentally” by the German chemist Karl Claus in 1967, when he licked his finger to pick up a piece of paper. It is 200 times sweeter than sucrose, but also has a discernable after taste.

Aspartame is widely recognized as the sugar substitute in the “blue package” sold commercially as Equal. It was “discovered accidentally” in 1963 by a medicinal chemist who was working on a drug candidate for ulcers. Aspartame is 200 times sweeter than sucrose, and has been one of the most widely used artificial sweeteners for diet drinks.

Aspartame is a relatively simple compound, being composed of two naturally occurring amino acids, aspartic acid and phenylalanine, which are identified in Table 5.2. In the body, the bond between them may be cleaved with resultant release of phenylalanine, which is converted into "brain chemicals" that can penetrate the blood-brain barrier. This can be particularly problematic for people with a condition known as phenylketonuria. This breakdown of aspartame increases as the temperature is raised, thereby negating its use in cooking.

The USA Food and Drug Agency was skittish about aspartame, approving it for human consumption in 1974 and rejecting it a year later, and into the Carter Presidency. The confusion of the manufacturer, G.D. Searle, was understandable. But after the Carter Administration fell, Donald Rumsfeld, the CEO of G. D. Searle, joined the Reagan Administration, and the prohibition was lifted by the FDA.

The problem with the sweetner could probably be solved by replacing phenylalanine with look-alike amino acids. This resulted in structures **alitame** and **neotame** being synthesized and tested. As Table 5.2 shows these compounds are very much sweeter. At 13,000 times sweeter than sucrose, just one speck of **neotame** should be enough to sweeten a cup of coffee.

Steviol, which occurs in the leaves of stevia shrubs, has been harvested for centuries by South American indigenous people. The compound is about 300 times sweeter than sucrose and has been approved by the United States Food & Drug Administration for use in foods.

5.2 A Comment on Splenda – And "Safety"

Implicit in the question about "safety" of Splenda is the assumption that if a sweetener is "natural", it is *ipso facto* safe. The syllogism that leads to this conclusion is a prescription for disaster. If a lover of mushrooms decides to venture into a forest and eat any mushroom encountered, he or she should make sure to have a will in place ahead of time.

Admittedly sucrose will not poison someone; but a diabetic who is constantly eating sugar in large quantities could lose a leg or two.

Safety of food is an arresting topic of discussion for newspapers, traditional and tabloid, blogers, health martinets, and the like. Prophesying Casandras feel free to dispense predictions that are totally unburdened by scientific evidence. A high school friend, to whom I had recommended Splenda as an artificial sweetener, contacted me in dismay because he had read on the Internet that Splenda "has chlorine in it". The article drew parallels with chlorine in swimming pools and washing machines to emphasize the outrage. This news induced a vision of ingesting household bleach, suitably disguised so that it would not be discovered, as Splenda is added to a cup of coffee. Our friendship was therefore imperiled.

My wife, daughter, nieces, nephew, and grandnieces are among the many who would also be endangered, because they are faithful users of Splenda – upon my recommendation. What is worse, is that my credibility may be suspect, because I do not use Splenda! I have been faithful to Sweet and Low (saccharin) for over 40 years.

So to put my friend's mind at ease, I asked if he put salt on his food to which he replied in the affirmative. I told him that according to the alarmist's logic, one could say that salt has chlorine in it. The same would be true for popular medications such as cozaar, diazide, triamterine HCTZ, dimetapp and chloral hydrate. Would the woeful Cassandra claim that these substances contain bleach? Consumers of Splenda can be assured that McNeil nutritionals, which formulate Splenda, are constantly subjecting their product to *independent* testing.

First, it should be noted that Splenda contains only 1% of the sweet agent sucralose. The remaining 99% is a carbohydrate known as maltodextrin which is a widely used "filler" or "thickener" in various medications, foods and the like, and its safety has been firmly established over several decades.

Second, we should take an elementary look at what happens to sucrose in the human body: As shown in the below in Fig. 5.2, sucrose is split by an enzyme into its constituent monosaccharides, glucose, and fructose. Further enzymatic activity converts glucose into fructose after which a cascade of enzyme-controlled processes results in breakdown of fructose. This process is accompanied by the liberation of energy which we can use to eat, sleep, or just to stay alive. If there is an excess of energy, as in the case of couch potatoes, it gets stored for a "rainy day"

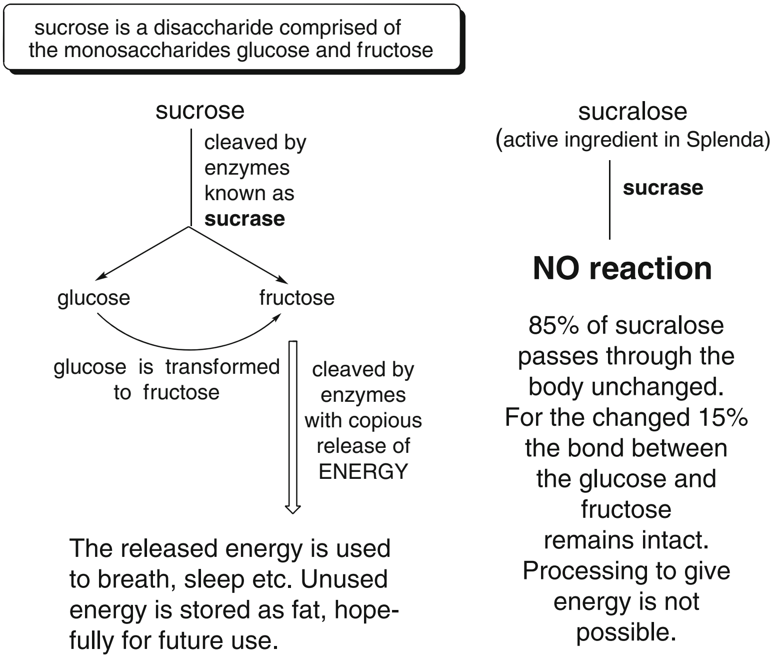


Fig. 5.2 Biotransformation of sucrose *versus* sucralose (aka Splenda)

when we need it. One form of storage is as a complex sugar called glycogen; but unfortunately, there is another form of storage that is visible to the naked eye. It is commonly known as fat.

(In Appendix **C** we give a more structural description of the above user-friendly enzymatic degradation of sucrose).

Sucralose simply does not respond to the enzymes that cleave sucrose. It is therefore not capable of providing a source of energy, nor of being retained in the body in the form of fat.

What is more noteworthy is that 85% of the sucralose that is consumed passes through the body, and can be recovered unchanged from urine and feces (ugh!).

The missing 15% undergoes transformations, **but the intersaccharide bond is not broken** and therefore that 15% is also excreted with no chance of being processed and stored as fat.

So whether Splenda "tastes like sugar" or not, it certainly does not behave like sugar. There is further support for this circumstance. As every cook knows, when sugar is heated, it becomes a gooey, caramelized substance that is sold as "browning" for adding color to foods. This gooey substance is responsible for the color that helps to make cookies and pound cakes look so appealing. Splenda (sucralose) does NOT caramelize upon heating, and so a pound cake made with it, may have the complexion of raw dough – definitely uninviting, albeit low-calorie.

This resistance to heat gives Splenda a major advantage over other high intensity sweeteners, since it can be used for cooking.

Chapter 6
“Luck?”

6.1 Serendipity and Discovery

“Anyone who can predict how sweet a molecule is will make a lot of money”.

This is the first sentence of the Abstract to an article entitled “The shape of sweeteners to come” by Leslie Hough and John Emsley (*New Scientist,* **1986** , *June 19).* The article and our discussion regarding the sweeteners in Table 5.2, testify to the essential role that serendipity plays in discovery. The often-used words “discovered accidentally” beg the question as to whether a discovery could ever be intentional!

In any event, the long history of scientific discoveries reveals that, “good luck” often plays an absolutely pivotal role. However, this admission does not devalue the achievement; instead it enhances it because the scientist(s) must have possessed the intuitive wisdom to recognize the significance of the event that just “happened”. This in turn, requires an informed mind, and equally well, the determination to prosecute the event. Thus there is more to it than luck.

Some people react with shock when told of the rationale behind the early experiments *en route* to sucralose (and thence Splenda). Professor Jones at Queen’s University, Canada, was hoping that a chlorinated derivative of sucrose would lead to a biodegradable pesticide. Simultaneously, Professor Leslie Hough at King’s College, London was hoping that chlorinated sugars would provide superior intermediates *en route* to antibiotics. Interestingly, these were not wild dreams. Indeed they were rooted in skilled speculation.

Thus it is instructive to place Jones’ ideas in the proper time frame – the late 1950s. The pesticide DDT, while excellent for exterminating mosquitoes, bed bugs, cockroaches and the like, was found to be problematic by Rachel Carson. The molecule accumulated in water, and caused the death of fish.

The basic problem was that DDT is not water soluble, and so does not decompose in nature – i.e. it is not biodegradable. DDT is a highly chlorinated molecule with 5 chlorines bonded to carbons. These bonds are very strong and are not prone to biodegradation.

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_6, © Springer-Verlag Berlin Heidelberg 2012

Jones' interest merged with a fortuitous circumstance. In the 1950s there was a world surplus of sucrose due mainly to the emergence of sugar beets as a more ready source of sucrose than sugar cane (see Chap. 4). Sugar processors, on both sides of the Atlantic, were anxious to explore new uses for the product, and generous funding was available for out-of-the-box investigations under the rubric of "Sucrochemistry". Jones probably reasoned that sucrose has 8-OH groups, which are responsible for its solubility in water. If some of these-OH groups were replaced by chlorine, the resulting molecule would still have enough-OH groups to be soluble in water – and hence to be biodegradable in rivers.

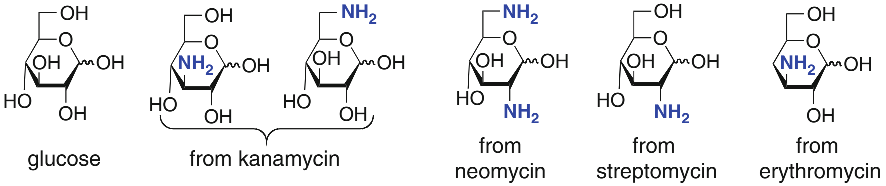
Hough's ideas were also founded on a real requirement, then and now, of the pharmaceutical industry. Many antibiotics contain modified sugars, and the most common modification is that one or more of the sugar's hydroxyl groups have been replaced by nitrogen. Examples of some such sugars, and the parent antibiotics, are seen in Scheme 6.1. In the 1960s, carbohydrate chemists were frantically replacing sugar-OH groups with nitrogen (more correctly amino) groups in the hope that they would get lucky, and be rewarded with a new blockbuster antibiotic. This was certainly true for the author's research group; but none of our products showed much promise.

Unfortunately, direct replacement of an OH group by an amino group is difficult. The process needs help, and chlorine provides excellent help. Accordingly, Dr. A. C. (Dick) Richardson, Hough's second-in-command at King's College London, had developed thoughtful, efficient procedures for introducing chlorine. Indeed the THREE chlorines in structure **H** (Scheme 4.1) had been installed by use of the Richardson strategy.

(This piece of chemistry is outlined in Appendix **B**).

That chlorinated sucroses turned out to be sweet rather than intermediates for pesticides or antibiotics, exemplifies the magic of serendipity. This also holds for the sweeteners in Table 5.2 which were "discovered accidentally", giving further support to the value of serendipity in science.

Similarly, the graduate student who discovered cyclamate may have been "lucky" that his cigarette came into contact with something on his lab bench. But had he not (a) been alert to the potential of the observation, (b) traced the origin of the sweet substance, and (c) subsequently devoted 15 years to its prosecution, the observation would not have been leveraged into a discovery. It is possible that several potential sweet substances may have been encountered over the years



Scheme 6.1 Some "modified" sugars found in antibiotics (The above are amino, or more correctly, deoxyamino sugars)

"accidentally" by chemists who were so focused on the job at hand, that they could not take time to investigate the "accident". The author does not like to dwell on this possibility, because he might incriminate himself.

Indeed, such "accidental discoveries" are scattered throughout the pantheon of science. One contemporary example is AZT, the first drug used against HIV. The compound had been 'rationally designed' years earlier for treatment of cancer. It was a complete failure for that purpose, and the compound lay in wait "for the right disease to come along", as the person who synthesized it first, biochemist Horowitz, told the *New York Times.* Eventually HIV came along!

Many anti-HIV drugs are modifications of AZT.

In a sense, the artificial sweeteners in Table 5.2 had to be "discovered accidentally" because from the structural point of view, it is evident that the compounds have nothing in common that would suggest a pattern of sweetness. But obviously, there must be "something" that confers sweetness on them – and it is that "something" that fascinates sensory scientists interested in the sweet response.

6.1.1 I Can't Believe He Tasted It? And He Was Smoking in the Lab?

Today's graduate students will be horrified to know that their predecessors could have been smoking cigarettes in the lab while carrying out experiments, or that they could have licked a finger! Wasn't he wearing gloves? Would he or she have deliberately tasted an unknown substance?

In this regard the following extract from a letter from Professor Hough is useful.

> "Phadnis thought he said "taste"—so he tasted it"—EUREKA!
> "Tasting was O.K., spit it out then wash out your mouth.
> "Dick & I tried it out in a cup of coffee – no problem"

Thus there was (is) a "proper" way to taste a new chemical – and also to smell it. Indeed, such definitive tests were used routinely by the author's generation, and we were taught HOW to taste and smell properly. Thanks to these lessons the author has survived tasting lead acetate (to prove that it is sweet) and smelling hydrogen cyanide – so as to recognize it, and hydrogen sulfide (rotten eggs), whose presence, fortunately, makes itself known.

With regard to smoking, we all smoked everywhere – in the lecture rooms and in the labs. A good question is 'What happens when a colleague was working with inflammable solvents such as diethyl ether and hexane?' As a point of common courtesy, such a colleague would be expected to alert the entire laboratory about his or her intention to use an inflammable chemical, thereby giving the smoker time to extinguish the cigarette safely.

Flipping it into the sink was not advisable, as one of my professors unintentionally demonstrated.

Fortunately today there are less risky test protocols, and so chemists, like sensible people, are cautious about what they put into their mouths. And in current laboratory practice, chemists uniformly wear gloves, and smoking in lab itself, indeed in the entire building, is forbidden.

Does this mean that the time-honored method for discovering new sweet substances has come to an end?

Chapter 7
Prepping for the Trial – Swords of Damocles Shall Dangle

7.1 This is Not "Law and Order" or "Perry Mason"

On TV shows like *Law and Order* or *Perry Mason* (for my generation), events taking place in the court room under the stern, downward gaze of the judge are given prominence over back-room squabbles between petulant lawyers. As an Erle Stanley Gardner aficionado in my youth, I was therefore not prepared for the depth and breadth of pre-trial haggling, bartering, and charged negotiations that took place by exchange of "briefs" that were not brief, frequently without the judge having to make an intervention. These pre-trial skirmishes served to narrow the perimeter of the case, refine the grievances, eliminate contentious issues of lesser contention, thereby saving the judge's precious time – not to speak of the expense of assembling the phalanx of lawyers, paralegals, court officials and other functionaries needed to balance the scales of justice.

In Hollywood court cases, where a jury is usually involved, the prosecutor – the District Attorney in Perry Mason cases – "examines" his witness, laying out the grounds that the witness will cover. The opposing (defendant's) lawyer (i.e. Perry Mason) then cross-examines the witness, confining the questions to the grounds laid out in the examination (although Perry would never be shackled by such niceties).

Law and Order devotees will be surprised to know that when a jury is not involved, the engaging spectacle of "examination followed by cross-examination" may be abolished. Some judges, notably Judge Bullock who would preside over the upcoming trial, require that the witness be examined by his or her attorney in the attorney's chambers, i.e. out of public view, by way of questions and answers that are designed to sharpen the points at issue between "them and us." The transcript of this exercise, is distributed shortly before the trial begins, and all litigants will have read it before the witness takes the stand, so that the cross-examination can begin directly.

How post-modern!

Such a Witness Statement, was one of four documents that I had to produce in the 2 months preceding the trial. First, there was an Expert Report which was,

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_7,

presumably, to establish the credibility of my credentials. This would of course elicit challenges from the other side's experts, some of whom were to prove so persnickety that they even corrected my use of "principle" for "principal" – or vice-versa (I can't remember which) – in one of my documents.

I thought it wise to get an early start, and so I decided to seek guidance from an obvious place, the Internet, on how an Expert Report should be constructed. The number one tip was: "be honest."

Be honest! Really! Well yes, because at this stage in our preparations, all of the Experts for both sides had been identified, and because the carbohydrate chemistry fraternity is comparatively small, we happened to know one another fairly well. Therefore, any unsupported aggrandizement of myself would be noted, and conveyed to the Complainant's (their) lawyers, who would surely rip off my emperor's clothes at a crucial moment of the trial. So, "be honest" was indeed the best policy.

So I got busy preparing a draft of my Expert Report. I began by detailing my academic training, starting with my undergraduate summer internship in the lab of Professor J. K. N. Jones, a world famous carbohydrate chemist, and earning my Ph.D. with supervision of Professor Ray Lemieux, another world famous carbohydrate chemist, my receipt of the Haworth medal, the world's *premiere* award in carbohydrate chemistry, etc. etc. Fortunately, just as soon as I was getting ready to dig up my sophomore grades, I came upon another piece of Internet advice that *should* have preceded the "be honest" admonition: "Talk to your attorney first."

My lead attorney was Gary Hnath then of the firm Bingham McCutchen. "We" represented Guangdong Food Industry Institute (GDFII) one of four Chinese Companies that were being charged with patent infringement. Gary assigned a young colleague, Goutam Patnaik (Gooch), to be my personal mentor – and tormentor. He began by throwing out all that stuff about my undergraduate internship. Instead, he formally introduced me to the "relevant legal principles."

This formal introduction raised my level of anxiety, because my daughter and her husband are both attorneys, she a trade lawyer and he a litigator. "Stop Bert," my-son-in-law once shouted as I was about to discuss an aspect of the case. "What you are about to say is 'discoverable' and so I cannot listen any longer." In consternation I asked, "If talk to Lillian, my wife, about the case, is that also "discoverable"? "Yes." Well, I surely did not want our case to be thrown out because I had blabbed to the wrong person. And so I soon learned to whom I could speak, and to whom I should not.

7.2 Patents, Bloody Patents

The writer may as well be honest and confess that the very thought of patenting a piece of work makes me run for the hills. This is probably because I have never earned a dime from the few patents that have resulted from being closeted with lawyers for hours. (In the interest of full disclosure, I must repeat that my daughter and her husband are both lawyers). But then, I probably have myself to blame for this. There are occasions when I have found, to my chagrin, that a procedure which

I had published some years earlier, was being exploited by a for-profit company – for making a profit! AARGH! Had I patented it, I might be rich!

But as a young university professor, my aim had been to publish my work as soon as possible, so as to pad my *Resume*, attract invitations to lecture here and there, and of course, to get promoted. The University patent office, on the other hand, wanted me to revise this, and restate that, and draw those diagrams differently, etc. However, lest it be thought that the patent office at my then institution, the University of Waterloo in Ontario, Canada, is sluggish about patenting, I must point out, in its defense, that the University was the mid-wife for Research In Motion (RIM) which invented the Blackberry. Maybe if I had invented something useful, they would have shown more enthusiasm!

The purpose of a patent is to secure your territory. Jonas Salk famously did not patent his anti-polio vaccine. He must have felt pretty secure about his territory. Less secure practitioners file patents, and to give added protection they usually exaggerate the boundaries of the invention so that all alternative approaches to it, actual or imagined, are "covered".

This may seem slightly improper, but it can be rescued, in my mind, by the concept of "obviousness". In other words, if a result is obvious, why bother to do the experiment?

So the Patent Office is confused – and confusing. If you say to them:

" I want to patent this today – but I am not going to do the experiment until next week. It will work – No Problem!"

"Get lost! Do the experiment first."

Two weeks later you come back and say:

"We did the experiment as you demanded. It works – so we want to patent it". "Get lost! It was obvious."

"Obvious to whom?"

"One-of-ordinary-skill-in-the-art".

"Such as whom?"

"Someone with a Master's degree in Chemistry"

"Oh! - Such as my jazz musician friend who goes all over the world showing that he is "one-of-ordinary-skill-in-the-art", and can do this but not that.?"

I didn't add that in private conversation, he had told me that working with carbohydrates was like beating his head against the wall – because it felt so good when he stopped.

And the patents in this case are about carbohydrate chemistry. This is a branch of organic chemistry, that is the bane of pre-med students. A colleague once claimed that he had saved more lives than Pasteur by flunking pre-meds.

7.3 The "Allegedly" Infringed Patents

There are three patents (463, 551, and 969) that the trial was about. In my view, the 463 was dominant. The chemistry in patents 551 and 969 is outlined (for chemists) in Appendix **E**, along with three expired patents (869, 476 and 746) that were issued between 1982 and 1985. They are included in Appendix E because of their historical importance to the trial.

The Tate & Lyle study in Table 5.1 (Sect. 5.1.2) revealed that sucralose is the sweetest of the nine chlorinated sucrose derivatives that were tested (tasted!). This is exactly the same as structure **H** (Scheme 4.1) that had been obtained 'accidentally' by Khan's group 2 years earlier (see Sect. 4.1.2). It had not been "tasted" at that time, so its sweetness had not been discovered.

(*The technical name of the sweet substance (before they knew it was sweet) was: "1',6'-dichloro-1',6'-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside". This was changed (after they found that it was sweet) to "4.1',6'- trichloro-galactosucrose (and thereafter TGS). When the product moved into the hands of non-chemists at Tate & Lyle and McNeil Specialty Chemicals, the name **"sucralose"** was invented).*

Since sucralose is 600 times sweeter than sucrose (not 2,000 times as stated initially by Tate & Lyle – see Table 5.1) only "a few grains" would be needed to sweeten a cup of coffee. Rather than sell a few grains of sucralose, Tate & Lyle engaged McNeil Specialty Chemicals, a subsidiary of the United States giant, Johnson & Johnson, to formulate sucralose in such a way that one teaspoon of the formulation would be equivalent to one teaspoon of sugar.

McNeil's formulation is marketed as SPLENDA. This formulation contains only 1% of sucralose. The other 99% is a filler (see also Sect. 5.2).

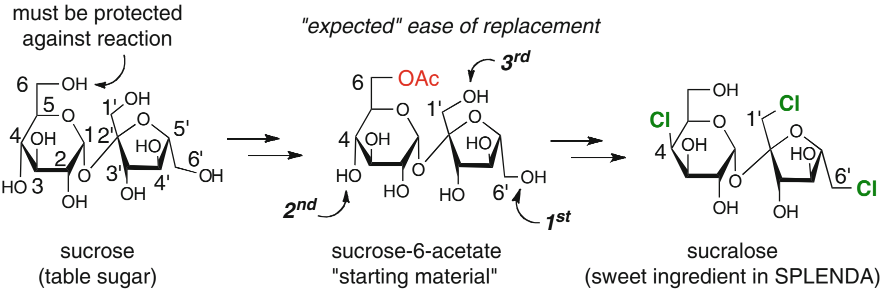
7.4 Patent 4,980,463 (the 463 Patent) – The Lynch Pin

Inventors: Robert E. Walkup, Juan L. Navia, Nicholas M. Vernon
Filed: Jul. 18, 1989
Issued: Dec. 25, 1990
Assignee: Noramco, Inc. Atlanta, Ga.

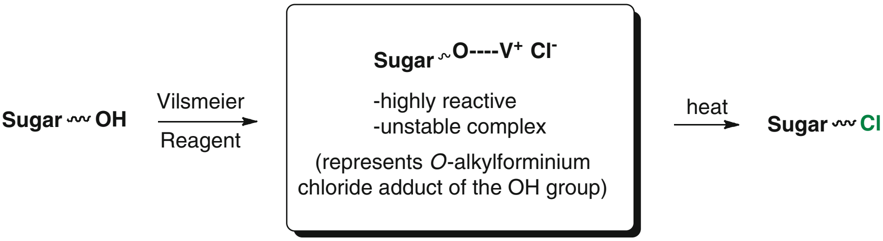
According to the then existing laws, patents were viable for 17 years from the date of Issue. The 463 patent would therefore expire in 2007, just when the trial would be taking place. *Interestingly **this** soon-to-expire patent would prove to be the lynch-pin of the trial.*

The legal battle between Tate & Lyle and the Chinese manufacturers, was all about chemistry, and chemistry requires drawings. Chemists, it has been said, have a gene that makes them walk around with pens in their pockets. This is because "a picture is worth a thousands words". Chemists therefore to communicate by means of drawings such as those shown in Scheme 7.1 which is a post-modern, minimalist, reductionist summary of several years of work.

The starting material is ordinary table sugar, and whether it is of the brown or white variety, it is the same substance known chemically as sucrose. The desired end product is sucralose which is the sweet ingredient in SPLENDA. Notably, position-6 is NOT to be chlorinated, because from Table 5.1 (Sect. 5.1.2) it can be



Scheme 7.1 A minimalist overview of the 463 patent



Scheme 7.2 A reductionist view of the Vilsmeier chlorination reaction

deduced that chlorine at position-6 DEPRESSES sweetness. Position-6 must therefore be "protected" at the outset, and this is the role of the red Ac group. Sucrose-6-acetate is therefore the effective "starting material". The minimalist diagram in Scheme 7.1 shows that THREE of the seven sucrose-OH groups are to be replaced by chlorine. These are shown in green in sucralose. The relative ease of installing the three chlorines is indicated in *italics.*

If the three-OH groups were equally easy to replace, there would be no problem; but that is not the case. Some challenging chemistry would therefore have to be developed. (This is described fully in Appendix **E**).

In spite of the "expected" ease of replacements indicated in Scheme 7.1, none of the three-OH groups is happy about leaving – and so a bribe needs to be offered. The bribe takes the form of the Vilsmeier reagent which, as indicated in Scheme 7.2, latches on to the-OH group to give a highly reactive, unstable complex. Application of heat induces a sequence of reactions which, at-the-end-of-the-day, results in chlorine replacing the sugar's-OH group.

Professor Stephen Hanessian, who incidentally was also an Expert Witness at the trial for one of the Chinese manufacturers, introduced the Vilsmeier Reagent for use in sugar chemistry in 1967. Dr. Riaz Khan (Sect. 4.1.2) adopted the reagent for his work on sucrose published in 1975. *(A more challenging version of the reaction mechanism, than that shown in shown in Scheme 7.2, will be given in Scheme 7.4)*

(Readers might like to know that the Vilsmeier reagent makes use of a chemical called dimethylformamide (**DMF**) which is a widely used industrial solvent. It is called a ‘polar aprotic solvent’, which tells us that it dissolves, or dissolves in, a wide range of substances – sugar, oil, water, nail polish remover, etc. In many respects, it is like DMSO (or dimethylsulfoxide), fortunately not as stink. As many people know, DMSO will dissolve medications and the resulting solution can be applied to the skin over an aching joint. Skin is like oil, and therefore repels water; thus we are able to shower without dissolving. But the DMSO can penetrate the oily skin, taking the medication with it into the body which, by the way, is mainly water. So the drug dissolves in the bodily fluids, and hopefully assuages the pain of the aching joint).

DMF serves as the solvent for the entire chlorination process of the 463 patent. One of the elegant aspects is that in addition to being the solvent, DMF also serves as one of the ingredients that is used to obtain the key Vilsmeier reagent for the chlorination reactions.

7.4.1 The Claims – The Dangling “Swords of Damocles”

The validity of a patent rests on the claims that it makes. These claims are usually summarized in an Abstract at the beginning of the document; but the “meat-and-potatoes” are found in the last pages, and are preceded by copious verbiage intended to provide a buttress against rejection by the Patent Office.

And so Gooch made sure that I understood the implications of the claims of the 463 patent which can be summarized in the following three points, two of which were to prove critical:

(i) —“adding at least **seven molar equivalents** of an acid chloride to a reaction mixture containing—[sucrose-6-acetate]*—and [the ingredients]—to form initially a **chloroformiminium chloride salt** –[i.e. the Vilsmeier reagent]—which subsequently forms a complex with the hydroxyl groups of the —[sucrose-6-acetate]—” (as depicted in Scheme 7.2) (emphases added). *(NOTE: The generic sucrose-6-ester is replaced with the specific sucrose-6-acetate for the sake of convenience and consistency).

(ii) The reaction mixture is heated “to an elevated temperature not higher than about 85°C for a period of time sufficient to produce a mixture ” — of products. **One of these contains two chlorines – at positions 1’& 6’.** (emphasis added).

(iii) Further heating at a temperature not higher than 125°C completes installation of all three chlorines.

Now this is supposed to be about chemistry and not about language, and so I blame my school-teacher parents for my pickiness; but the underlined phrase in claim (i) should have been:

“forms complex**es** with the hydroxyl groups—”;

OR

“forms **a** complex with **one of the** hydroxyl groups”—

This grammatical contention seemed rather trivial at the time, but the question of whether ALL of the seven-OH groups of sucrose-6-acetate, or only some of them, form complexes during the Vilsmeier reaction, was to be of crucial significance *on the very last day of the trial – with me on the witness stand.*

So as it turns out there was good reason for me to be pedantic; but back to the patent.

7.4.2 Sword #1 Mufti/Khan Did It Before. Therefore It's Not Novel

Ignoring my pickiness, claim (i) can be understood to say:

The sugar to be chlorinated, and all of the ingredients needed to prepare the Vilsmeier reagent, are mixed together at the start.

This rendition emphasizes the problem. In 1983, US patent No: 4,380,476 was filed by Inventors Khizar S. **Mufti**, and Riaz A. Khan with assignees as Talres Development, (a subsidiary of Tate & Lyle). This Mufti/Khan patent stated:

"**the reagents may be formed in situ**, but are preferably prepared in advance and isolated before use."

The implications of the seven highlighted words in the foregoing sentence were fraught. It could be argued, and indeed was, that these words provided a precedent for claim (i) as summarized in **bold** italics above. Highly paid lawyers would therefore try to convince the judge that the two above highlighted statements had totally different meanings.

7.4.3 Sword #2 The Office Action

And then Gooch brought forth the dreaded "Office Action."

These documents usually are issued after the Patent Office has deigned to peruse the submitted patent application. Rather than laugh in your face, they use the Office Action to say something like "It will be a cold day in hell before this is okayed".

Of course, lawyers for Tate & Lyle, the assignees of the 463 patent had spared no effort to prevent lowering the temperature in hell. Their attempt to rebut the Office Action said:

(a) "—the—[Vilsmeier reagent]—is generated by the reaction of an acid chloride with a tertiary amide **in the presence of sucrose-6-[acetate]"**—and
(b) "—the chlorination is carried out in distinct phases at different reaction temperatures."

Not surprisingly, these 'clarifications' raised new problems:

The first, (a), did not ameliorate the conflict of the 463 patent with the 1983 **Mufti** patent. Indeed it cemented their similarities.

The second (b) opened a new “can of worms.” The phrase implied that the heating was not increased continuously, but in discrete steps. However a Deposition by a Tate & Lyle worker, taken before the trial, stated that the heating was continuous – not stepped.

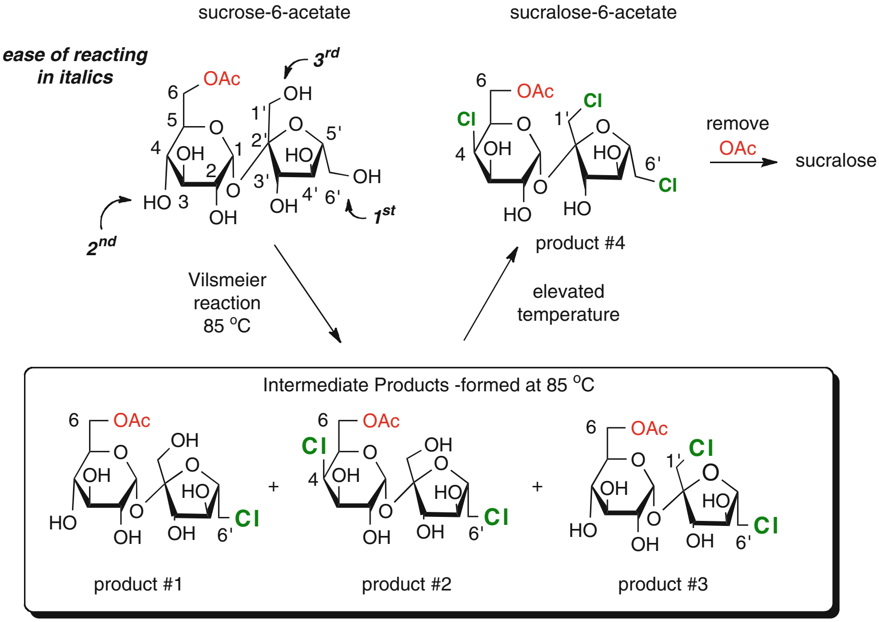
So what does it matter! The chemical transformations would take place whether the heating was stepped or not!

For patent lawyers it matters a lot, because if a patent is not practiced according to its claims, it is invalid, and therefore cannot have been infringed.

7.4.4 Sword #3 What is Proof?

Claim (ii) of the 463 patent says “—subjecting the reaction mixture product of–[the first]–step to an elevated temperature not higher than about 85°C for a period of time sufficient to produce a mixture consisting essentially of”—[**products #1, #2, and #3**, Scheme 7.3].

So product **#3,** which is supposedly formed at 85° has two chlorines - at positions 1’ and 6’. This posed a BIG problem, because from the standpoint of the actual lab procedure, position 1’ is very, very, very unreactive. Chlorination was therefore not expected at the low temperature of 85°.



Scheme 7.3 A more detailed look at the 463 patent

We therefore wanted to know more, about this interesting piece of chemistry,

What was the PROOF that the compound was really **product #3**?

And here the differences between "proof" in chemistry and the law would be explored in Judge Bullock's court room.

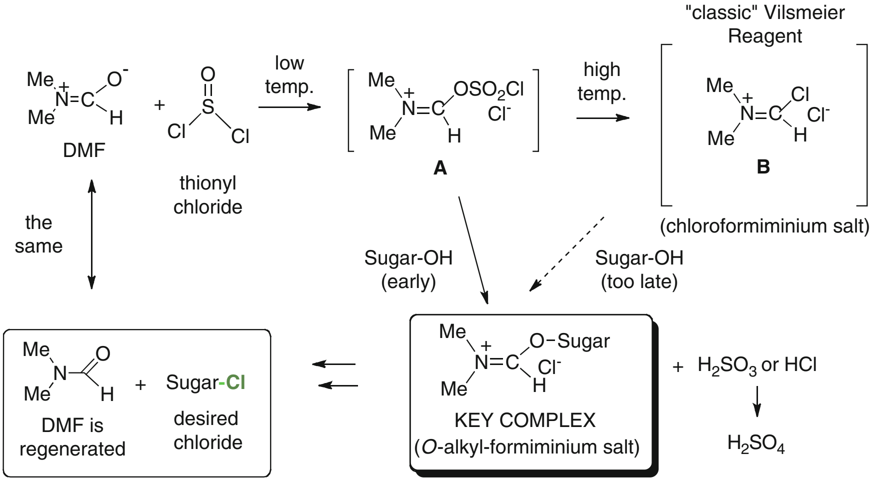
And all the while, the Swords dangled.

7.5 What's Going On? (With Apologies to Marvin Gaye) The Vilsmeier Battle

Thanks to Gooch, my Expert Report was excelling at nit-picking—and there was more.

There is this phrase in the Abstract to the 463 patent: "—to form **initially** a chloroforminium chloride salt—". This "salt" is the "classic" Vilsmeier Reagent, **B**, in Scheme 7.4. The reductionist version of the Vilsmeier Reaction in Scheme 7.2, will now have to be expanded to what is shown in Scheme 7.4.

The salt **B** is identified in Wikipedia as the Vilsmeier Reagent, and it is sold under that name by chemistry supply houses – notably Aldrich. However questions about its formation have engaged investigators over the years. Several reports contend that dimethylformamide (DMF) and an acid chloride, thionyl chloride in this case, unite to form **A** at low temperatures, and **A** is then converted to **B** at higher temperatures. This sequence is supported by an elegant experiment, done nearly 20 years ago, which showed that the "intermediate **A**" (i) was stable for a very long time, (ii) could be used at lower temperatures, and (iii) was better than the salt **B** for carrying out certain chlorination reactions.



Scheme 7.4 Battle of the Vilsmeier reagents

And so I proposed that intermediate **A** would react with the alcohol, Sugar-OH, to give the "**KEY COMPLEX**", while the temperature was still low, without having to wait for the salt **B** to form at higher temperatures.

In short, intermediate **A** could function in the traditional Vilsmeier mode as a chlorinating agent. However this language was not favored by Gary Hnath, the senior lawyer in the case. He preferred that the word Vilsmeier be confined to its use in the 463 patent.

And I subsequently understood that this made for better lawyering.

From the standpoint of *chemistry*, it would not matter whether the intermediate **A** or solid **B** reacted with the alcohol (Sugar-OH) to give the **KEY COMPLEX**, because the **desired chlorinated alcohol** would be formed either way.

But from the standpoint of *law*, it made a whole lot of difference. If the temperature was too low for "salt" **B** to form, *and the word "salt" is used in the claim (i),* then there would be no grounds for an infringement challenge.

Our legal team therefore sized upon these nuances and proposed that the effective reagent for our Chinese clients, at the operating temperature of the GDFII factory, was the "intermediate," **A**, under conditions where the salt **B** would not have yet been formed. **Thus there could be no infringement.**

This nuanced interpretation was incorporated into my Second Expert Report, in which I included a diagram of Scheme 7.4. The Expert Report elicited the expected written response from the Complainant's lawyers; but it also included a rendition of the diagram in my Expert Report, professionally embellished and more picturesque. Of course there was no acknowledgement of me as the source of the idea. However more importantly, it did not disagree with the content.

7.6 The 551 and 969 Patents

Patent 5,034,551 (the 551 patent)

Inventors: Nicholas M. Vernon, Robert E. Walkup
Filed: Apr. 23, 1990
Issued: Jul. 23, 1991
Assignee: Noramco, Inc. Athens, Ga.

and

Patent 5,470,969 (the 969 patent)
Inventors: George H. Sankey, Nicholas M. Vernon, Robert E. Wingard, Jr.
Filed: May. 2, 1994
Issued: Nov. 23, 1995
Assignee: Noramco, Inc. Athens, Ga.

The 551 and 969 patents describe procedures that introduce greater efficiency and cost-effectiveness than the 463 patent. These procedures are workman-like, rather than ingenious; but they accomplished their objective admirably.

(Fuller discussion of the 463, 551 and 969 patents is given in Appendix **E.** Expired patents 869, 476 and 746 are also discussed.)

7.7 My Deposition

My Deposition loomed. This generated the most anxiety of my pre-trial trials. For my Expert Reports, I could rely on the comfort of Gooch for friendly criticism; but now a lawyer from the other side would certainly be adversarial. I had been deposed once before some 40 years earlier. While living in Canada, my wife and I had taken our house builder to court, where we lost, because of a precedent in British Law dating back one or two centuries. We appealed and appealed and appealed, and after some years the case went to Canadian Supreme Court where it was resolved – fortunately in our favor. Today, Fraser-Reid versus Droumtsekas is taught in law schools across the British Commonwealth. I was quick to disclose my earlier Deposition, because it could be 'discoverable'!

As the date approached, visions of a private Spanish Inquisition took hold. My Deposition would be videographed for all and sundry to peruse. So there was concern about my appearance. My 20 year old suit still fit – if I omitted the vest, and left the jacket unbuttoned. Not good enough! So off I was taken by dear wife and meticulous son to Nordstrom where a shirt today can be as expensive as my suit was 20 years ago.

I left properly outfitted.

And least so I thought when I went to meet my Torquemada. Our lead attorney, Gary Hnath met me at a Starbucks *en route* to Finnegan Henderson's law office where my Spanish Inquisition was to play out. Gary seemed more anxious than me, and because the event would be videographed, the Marshal McLuhan dictum "the medium is the message" required that I look my very best for the cameras. Gary kept fussing with my tie, the blue checkered one that Lillian had bought at Nordstrom. He moved my tie clip up, and then down, and then finally out.

And my pens! As noted above organic chemists need their pens so badly that some students regard our "pens in the pocket" as evidence of a chemistry gene.

My genes notwithstanding, Gary thought that my pens would detract from the videograph and so out they went. Luckily my son had given me a modern pair of shoes for my Christmas present. Gary commented favorably of the fact that I was not wearing white socks. Little did I know that my customary athletic white socks had been noticed around the office.

In the event, my Deposition was not as traumatic as I had expected. My antagonist, or so I felt going in, was the same Mr. Fues who had headed the Inspection team in Guangzhou some months earlier. He did try to "mix-me-up", as my Jamaican compatriots would put it, but a Torquemada at a Spanish Inquisition, he was not. He even complimented me on my blue shirt. And since I was worried that the truth could be 'discoverable', I confessed outright that the shirt had been selected and bought by Lillian, my wife – at Nordstrom. At the end of the 2 day ordeal, a (kind of) relaxed Gary opined that I had hit a home run.

7.8 Visit to a Factory in China

At the heart of Tate & Lyle's patent infringement case, was the accusation that Chinese manufacturers were using a tin catalyst in the critical step for converting sucrose to sucralose, the sweet ingredient in Splenda. I had been told, soon after my appointment as expert witness, that I would be required to visit the factory of our Chinese clients.

This would be my second visit to China, but this time without my wife, Lillian.

For this visit, I was worried about the long flight from the United States to China because I had been suffering from severe back pains for which an epidural injection was scheduled a few days before I was due to leave. The fearsome 13 h-long transpacific leg from New York to Tokyo seemed less fearsome, when I discovered that I would be flying on Japan Airlines. I do not normally travel business class, but my fragile back needed tender loving care – and I got it in their business class. The seats could be converted by touch of a button into a horizontal cocoon that allowed me to be fully extended, and even to roll over from side to side. So I slept very well, and that was fortunate because the second leg, from Tokyo to Guangzhou, arrived at midnight. Nevertheless, I had to be ready to go at 7:00 am the next morning. I guess after flying business class, one should not expect the luxury of sleeping in!

The Guangdong Food Industry Institute (GDFII) factory is in the Southern province of Guangdong, in Guangzhou, a city of 20 million people, known formerly as Canton. The name is eponymous with the famous Cantonese food. This ancient city is of particular significance to Jamaicans, because many of the indentured laborers who were brought to the island by the British after the abolition of the West African slave trade (Sect. 1.2), hailed from this region of China. I recall that some of my schoolmates had brothers who suddenly arrived at the school from China. In spite of their fractured English, they were able to convey stories about exotic places and "strange" people and customs. This experience helped to expand my narrow Jamaican horizons.

In April 1998, my wife and I had the pleasure of spending 3 days in Guangzhou during a month long lecture tour of China. Our memory is of frenetic activity, buildings of every size and description being erected as far as the eye could see along the overloaded highway to Hong Kong, 100 km away.

For some buildings to be erected, others had to be demolished. This was accomplished, not by heavy machinery, but by a force of little men armed with nothing more than sledgehammers. But not your ordinary *everyday* sledgehammer. These sledgehammers had pliant handles. Thus as the worker swung his instrument, the pliant handle first arced backwards, and then forwards as he swiftly sent the heavy head crashing into the thing that was to be demolished.

The pliancy of the handle made all the difference, for it enhanced the power of the normal instrument by several orders of magnitude.

What an elegant demonstration of fundamental physics? What a smart way to provide work for poor, eager, strong men? What and ingenious invention? And what a danger to the worker's arse?

Because of the pliant handle, the backward arc must be controlled precisely, or the steel hammer would end up crashing into the worker's cocxy. But not to worry! The workers knew how to protect their at-risk tail bones. They controlled the backward swing by sliding one hand forward toward the head, releasing it judiciously before it wrought rearward disaster.

The university that was our host was originally the American Religious College, started by the early westernized National leader, Sun Yat-sen. The name of the Institution has since been changed to Zhongshen University which, very interestingly, was the alma mater of Dr. Wang, the Director of GDFII and Hellen Chunrong Li his assistant. They were glad to learn about my visit to their alma mater – albeit several years earlier.

By the time of my visit to China, I had thoroughly immersed myself in the chemistry leading up to sucralose, the Tate & Lyle patents at issue, as well as those that preceded it.

What of the Chinese patents? None were given to me!

Instead I had been provided with confidential information about the procedure that GDFII used for making sucralose. I was initially taken aback, because the chemistry seemed familiar. This was indeed the case, because their procedure shared many common features with Tate & Lyle's patent by inventors Mufti and Khan. But after some quick arithmetic, I relaxed because the Mufti-Khan patent was issued in 1983 and had therefore already expired. Indeed, the GDFII scientists deliberately chose to improve upon an expired patent, so as to protect themselves from the very infringement charges that they were now facing with Tate & Lyle.

But Tate & Lyle had good reason to be suspicious. Both Tate & Lyle and GDFII used the same starting material (namely sucrose-6-acetate, see Scheme 7.3). The Mufti-Khan procedure, that was used in the expired patent, had given only 7% overall yield. This was not good enough for use in a factory. The low yield was traceable to the "messy" preparation of their sucrose-6-acetate starting material. The difficulties were overcome by Juan Navia of McNeil Specialty Chemicals. Dr. Navia invented an elegant, concise route that, notably, employed a tin catalyst, that gave sucrose-6-acetate in over 95% (Appendix E, Scheme E5). At the time there was a partnership between Tate & Lyle and McNeil Specialty Chemicals (a subsidiary of Johnson and Johnson), which resulted in the commercial product now known as SPLENDA (see Sect. 5.2).

Since the Mufti-Khan process had given only a 7% yield , would the Chinese chemists be able to improve the yield to a level where it could be used for factory production? That was one of the questions that I needed to satisfy myself about.

The Chinese factory was, shall we say, rudimentary – but highly functional. It was totally open to the elements, with various reactors arranged on two levels. There were color coded pvc pipes, moving stuff up or down, around or in coils, that debouched in a timely manner into the appropriate vessel, some of the latter cooled by ice water, others heated by steam.

I asked Dr. Wang, the youthful director and chief chemist how long it took GDFII to build the factory, once they had decided upon the manufacturing process. I expected an answer of 12–18 months. I originally thought I had misheard the answer; but I had heard right. It took THREE months!

Each of the reaction stations was manned by a confident, intense technician, who was evidently in total control of his station. There was no evidence of automation. Coordination of the various stages of the manufacture therefore seemed to be under human control, rather than being orchestrated from a central, remote automated panel. Success therefore required great precision on the part of the technicians, and explains the need for an expert at each station. Thus, although the factory was rudimentary in its construction, it was efficient and purposeful in its operation.

On the other hand, the modesty of the plant could justifiably invite skepticism about the operation's sufficiency to compete with mighty Tate & Lyle. So the issue was joined. To check whether or not the Chinese manufacturers were using their patented tin catalysis procedure, Tate & Lyle had obtained a Court Order to visit and inspect the GDFII factory. My visit was timed to coincide with the arrival of the team of inspectors. Gary Hnath GDFII lead attorney, would also be present for the inspection on October 11, 2007.

The team of Inspectors was headed by Mr. Fues, an attorney with Finnegan Henderson, the Washington law firm that represented Tate & Lyle. The team included a young lady (a lawyer, as it turns out) who double checked everything, a videographer, analytical chemists from an independent commercial USA lab, shipping agents who would later have to catalog, separate, and ship the samples from China to the United States, and one or two other functionaries. At each station, the "Voice of the Inspection" (as I chose to describe him), would announce what we would be seeing, and how it could be correlated with the flow sheet that GDFII had supplied. The videographer would then videograph.

Naturally, the Inspection Team wanted to see the factory operating under "normal" conditions, even though there would be 20 strangers tramping around; but since the "normal" operation in this very Chinese factory is on a 24-h loop, GDFII had to change their manufacturing schedule to accommodate the wishes of Inspectors. Some samples were taken at 2 or 3 in the morning. Gratifyingly, I was excused from these early morning inspections since I was still recovering from jet-lag, having crossed the Pacific only a few hours earlier.

To detect any lingering traces of tin catalysts, members of the team swabbed the entry ports of several of the plant's reactors with gauze which had been wetted by some sort of solvent. Samples were also collected from pipes that traveled between two reactors, sometimes with dramatic consequences. At the best of times the air in the plant reeked of various chemicals causing many of the non-chemistry personnel to don gas masks. However, when the pipe delivering the Vilsmeier chlorinating reagent was sampled, the plume of sulfuric and hydrochloric acids that emerged, forced chemists and lawyers alike to rush for fresh air.

As the inspection progressed, the Inspection team seemed to get more and more frantic in their search for evidence that GDFII had indeed been using a tin catalyst. Their incredulous swabbing sometimes extended to the floor beneath the vessels! The hopefully incriminating tin-soaked swabs were then placed in a lock box, labeled and made ready for shipment back to the United States.

This search for the offending tin, struck me as rather desperate, in fact so ludicrous that it could be right out of a Woody Allen movie. First, the GDF11 manufacturing flow-sheet that had been supplied to all of us disclosed that they actually used a tin catalyst (tin chloride) at a late stage of the manufacturing process. But the Inspectors were apparently not worried about this, because tin chloride is an **in**organic substance, whereas the tin catalyst used in Tate & Lyle patents was organic tin.

The required proof was therefore made more difficult to obtain, since differentiation had to be made between inorganic and organic tins.

So just how widespread are organic tins in China? Top level legal firms have ready access to efficient research facilities and we, at Bingham McCutcheon, soon received a stack of publications about organic tin in China. They are EVERYWHERE, in PVC pipes, paints, plastics, lipstick etc. The literature noted specifically that the waters of southeast Asia were heavily contaminated with organic tin. China's Pearl River contains one of the highest concentrations of tin in southeast Asia. The GDFII factory stands on its banks, *and the river provides water for the factory's operations!*

Whether the swabs were capable of establishing the provenance of any suspect organic tin from these disparate sources remained to be seen.

Chapter 8
Preamble to the Trial

8.1 The "MATTER"

The legal proceedings in this report are reproduced from the PUBLIC VERSIONS OF THE HEARING TRANSCRIPTS:

In the matter of certain sucralose, sweeteners containing sucralose, and related intermediate compounds thereof for the trial before the United States International Trade Commission, FEBRUARY 20–29 2008, Investigation No. 337-TA-604, presided over by the Honorable Charles Bullock.

(A 337 investigations takes place if there is importation of products into the United States that competes unfairly with the domestic industry).

8.2 Reportage

The verbal dialogue between participants in the Court proceedings is taken directly from the transcript of the PUBLIC VERSON. Where necessary—[connecting phrases]— shown in square brackets, are used to condense the dialogue.

Quotation marks are used when the dialogue exceeds one paragraph.

Random, gratuitous comments and/or explanations by the author are inserted in italics.

To facilitate reporting of the trial discussion, complicated names of the relevant chemical structures, will be replaced with identifiers (e.g. "structure #2, Scheme 9"). This is also necessary, because the same structure is given different names by different participants in the trial.

Since the author was an expert witness for GDFII, issues affecting this manufacturer are given prominence throughout the report.

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DOI 10.1007/978-3-642-22781-3_8,

8.3 The Stage

The United States International Trade Commission, Washington D.C.

8.4 The Cast

The Judge was the Honorable Charles Bullock.

The complaintants (*Plaintiffs*) were the Tate & Lyle subsidiaries listed in Sect. 8.1. Their lead attorney was Mr. Tom Jarvis, ably assisted (mainly) by Messrs. Goulet, Barney and Fues, all of the firm of Finnegan, Henderson, Farabow, Garret & Dunner.

The chemistry expert for the Complainants was Professor David Crich.

The respondents (*Defendants*) included manufacturers, as well as packagers and distributors of the Chinese-made sucralose. The lead attorneys for the manufacturers who are named in this report were:

Ms. Marcia Sundeen of Kenyon and Kenyon for Hebei Sukerui
Mr. Craig Smith and Ms. Maria Hamilton of Fish Richardson for JK Sucralose
Mr. Gary Hnath and Mr. Goutam Patnaik of Bingham McCutchen for Guangdong Food Industry Institute (GDFII) (Niutang)

The Respondents' chemistry experts were Professor David Baker (Hebei Sukerui), Professor Stephen Hanessian (JK Sucralose), Professors Eric Walters and Bertram Fraser-Reid (GDFII and Nuitang).

The office of unfair import investigations exists within the International Trade Commission (ITC) of the United States. The Office is STAFFED by attorneys who participate in "Section 337 Investigations." **The Office functions as a neutral party representing the public interest.** The Office's role is unique, and its job is to make sure that the ITC has a full and complete record from which to make its decisions, providing a viewpoint that is not associated with any of the contending litigants. The Office does not take a position until just before the hearing begins, at which time a prehearing brief is filed which states a position on each of the contested issues in the case.

For the ITC Staff:
Christopher Paulraj
Anne Goalwin

8.5 The Documents

This patent infringement case was mainly about chemistry, so both sides had chemistry experts, each of whom was required to submit an Expert Report which established his/her competence to participate in the case at hand. The "other" side's expert would then eviscerate the document, and the first expert would have to respond with a second (or rebuttal) Expert Report. Both reports were prepared with the help of his/her friendly lawyer.

Subsequently, a deposition was inflicted upon the Expert Witness by a lawyer from the "other" side, who would eviscerated him/her once more – this time face-to-face, instead of in writing. His/her lawyer was also present, but could only make *pro forma* objections. These were duly noted in the transcript, and served to alert the judge, and whomever else, that an objection had been lodged.

There was no jury for this trial – just the judge. So rather than have a witness be **"examined"** in Court, there was a prior question-and-answer session with his/her friendly lawyer, which was recorded as the witness report**.** The document was sent to all concerned, so that in court the **cross-examination** of the witness would begin directly.

8.6 The 463 Patent Revisited: Again

NOTE: (1) As noted in Sect. 8.2, because the names of the chemical products are so complicated, the names have been replaced with structure identifiers such as indicated the Scheme 7.3.

(2) Although the generic sucrose-6-**ester** is mainly used in the 463 patent, I will instead be using the specific sucrose-6-**acetate**, which was the actual starting material used in the factory (see Scheme 7.3). An efficient synthesis of this material had previously been patented by Juan Navia (see Appendix **E**). Navia's use of a tin catalyst was critical to the success of his invention, hence the use of tin by the Respondents could be seen as evidence that they had been copying the Navia procedure.

Evidence relating to the use, or absence, of a tin catalyst was a major issue in the trial.

8.6.1 The "Recipe"

(To facilitate discussion of the recipe, please see Scheme 7.3).

Step (i): Sucrose-6-acetate is dissolved in dimethylformamide (DMF) and the solution is cooled.

Step (ii): **At least seven equivalents** of thionyl chloride are added and the mixture is then heated "not higher than about 85 degrees for a period of *time sufficient* to produce a mixture of products" consisting mainly of monochloro products, (***product#1****, chlorinated at the favored the position-6'*) and dichloro derivatives **products #2** and **#3**.

Step (iii): The temperature is elevated to 100–130 degrees "for a period of *time sufficient* to produce a product comprising predominantly of the trichlorinated compound" (sucralose-6-acetate i.e. **product #4**), the immediate precursor of sucralose.

8.6.2 Why the Fuss About Product#3? A Sword of Damocles?

As shown in Scheme 7.3, three chlorines are to be installed in going from the starting material sucrose-6-acetate, to sucralose-6-acetate (**product #4**). On the basis of prior work, the ease of the process was expected to be:

Position-6' easier than position-4, which is very, very much, easier than position- 1'.

According to this order, **product #3** could be seen as an anomaly because position-1' had been chlorinated whereas position-4 had not.

Technically to a chemist, anomalous formation of **product #3** would not be a big deal, as long as at-the-end-of-the-day, the desired material, **product #4,** was obtained.

But to lawyers, such an anomaly is grist to the mill because:

One of the requirements of a patent is that "someone skilled in the art" would be able to repeat the procedure. The problem is, if I wanted to repeat the procedure, how could I tell when *"time sufficient"* has elapsed, according to step (ii), so as to obtain **products #1, #2** and **#3**. And how could I tell if each is actually present? How would I *identify* each?

The anomaly of product #3 would therefore be one of the Swords of Damocles that hung over the Trial.

8.6.3 And Also About "In Situ"? Another Sword of Damocles?

The **Vilsmeier Reaction**, which was used in the manufacturing process, played a critical role in the trial, and the concept of the **"in situ"** formation of the reagent was

Consider the reaction of THREE components, A, B and C, where
the **reagent** is obtained by combining (B + C)

If we mix: (a) A + B OR
(b) A + C

there will be no available **reagent -** hence no product in either case. BUT

If we mix: (c) (A + B) then add C OR
(d) (A + C) then add B
} **the reagent is formed *in situ***

OR

If we take (e) (B + C) and add A **the reagent is NOT formed *in situ***

- there will be product in cases (c), (d), and (e) - BUT the **strategies** are different.
- In equations (c) and (d) the **reagent** is formed in the course of the reaction - in other words, ***in situ***.
- In equation (e) B & C are combined first, outside of the reaction mixture therefore the **reagent is preformed,** ***i****.e. NOT in the presence of A.*
Thus the **sequence** of addition is important

Fig. 8.1 What does "in situ" mean – to me?

a recurring “banana skin” under the feet of the witnesses at they were grilled by the Complainants’ counsels. My understanding of the term “in situ” is given in Fig. 8.1.

In the 463 patent, the mixture used in step (ii) already contains TWO of the necessary reactants, i.e. sucrose-6-acetate and DMF (the solvent). So this is like equation (a) or (b). Upon addition of the thionyl chloride (the acid chloride) we now have equation (c) or (d), and there will be an immediate reaction to give the Vilsmeier reagent. The situation is therefore “in situ” – by my understanding.

The “in situ” issue was another **Sword of Damocles** that dangled over the trial.

Chapter 9
Day One of the Trial

The trial started promptly at 10:00 am, on February 20, 2008.

JUDGE BULLOCK: On the record. Good morning. We are going to be starting—with the tutorial and then probably, hopefully, we will finish that by lunch break and then go into the prehearing conference. Let's start with appearances.

Here, "appearances" does not refer to whether the folks in the court look neat or scruffy, but to the lawyers who will appear before His Honor. I have listed the lead lawyers in Sect. 8.1.

9.1 Tutorials

The alleged infringements touched upon some fairly sophisticated pieces of chemistry. Tutorials were therefore given to the Court, on various aspects of the chemistry that would be encountered in the case, and these occupied the morning session.

The topics were divided up between the Expert Witnesses for the Complainants and Respondents. I do not know how these assignments were made, but it was my lot to present a tutorial on the chemistry of tin. Of course, nothing in litigation at this level proceeds without prior rehearsal, and so my power point tutorial was presented to an audience including Goutam Patnaik (Gooch), my coach, and Gary Hnath, the lead counsel for our Chinese clients, Guandong Food Industry Institute (GDFII) on the day preceding the Trial.

My rehearsal got off totally on the wrong foot. I began something like this:

"Good morning, Your Honor. The chemistry symbol for the metal tin is Sn which comes from the Latin word *stannum*. You will be hearing about organic tin and inorganic tin derivatives. These compounds can be very powerful catalysts, and both are used in the manufacturing processes that you will be called upon to adjudicate."

And then I continued.

B. Fraser-Reid, *From Sugar to Splenda*,
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“And so, Your Honor, I will be telling you about aspects of the chemistry of tin that will help you to understand the issues to be presented to you —.”

“Stop right there,” bellowed Mr. Hnath. “That sounds condescending.”

I am so glad that I had a chance to rehearse my speech, because I might just have insulted the Judge on the very first day of the trial. As it turns out, I was to eventually earn his rebuke – but not on the first day.

The first two tutorials before Judge Bullock were given by the Complainants, Tate & Lyle.

MR. BARNEY: Your Honor, our tutorial is going to be presented by two gentlemen, the first of which (*sic*) is Dr. David Crich.

Professor David Crich, a distinguished chemist, then at Wayne State University, had the formidable task of laying most of the ground work, not only for the Complainants, but for the entire trial. His tutorial ended up being a mightily condensed version of sophomore organic chemistry that would cover what organic chemistry is, what sucrose is, how compounds are named, etc. That was the easy part.

Considerable time in his tutorial was devoted to the sophisticated, fundamental general scientific theory known as the Maxwell-Boltzman distribution, which deals with collision of particles in the gas phase. This theory, when applied to chemistry, suggests that if particles collide with enough speed, a chemical reaction will take place. Hence there is a connection between speed (energy) of the collision, and possibility of a reaction. Maxwell and Boltzman were mathematicians, not chemists, and the high level of mathematics they employed can be enjoyed by visiting the pertinent Wikipedia page.

For those who do not have the taste for dense mathematics, I will attempt to provide a simplified analogy of the Maxwell-Boltzman distribution theory using a more accessible, and probably even familiar analogy.

Girl and boy, **A** and **B** respectively, live in different villages and do not even know of each other. Boy **A** moves to the village where girl **B** lives. They run into one another at the mall; (1) but that event is not enough of an incentive (energy?) for them to unite as **A-B**. They move in together; (2) but that development is still not enough of an incentive for them to unite as **A-B**. A baby is soon on the way; (3) but that is still not enough incentive for them to unite as **A-B**. The father of girl **B** arrives with a shotgun; (4) that provides the necessary impetus (energy) for them to unite as **A-B.**

Now for any boy and any girl on the street, it would be difficult to say which incentive, (1), (2), (3) or (4) would be required for them to unite. However, if you take several million boys and several million girls, it is certain that you would find one girl, **A,** and one boy, **B**, for whom *each* of the four incentives would induce them unite as **A-B.** The task then is to find them, wherever they may be.

If **A** and **B** were chemical entities, the incentive for them to unite comes in the form of energy. So, if you take several trillions of **A** and several trillions of **B**, there would exist (at least) one pair that would have enough energy to override their individual comfort zones, and unite as **A-B** even after the casual meeting in the mall. The shotgun would not always be needed.

The above is my simplification of the Maxwell-Boltzman distribution, not Professor Crich's. For his, see pages 20–30 of the public transcript of the trial (which is available on the Internet).

There would be other interpretations of the theory as the trial proceeded, and some of these will be described.

The second tutorial of the day was given by Dr. Walkup formerly of McNeil Specialty Chemicals, the Johnson & Johnson subsidiary that worked with Tate & Lyle to develop the formulation of sucralose which we now know as SPLENDA. He is one of the Inventors of the allegedly infringed 463 patent. Dr. Walkup, now a minister in the Presbyterian Church, outlined the various stages that culminated in Tate & Lyle's current efficient manufacturing process for Splenda.

The third tutorial, and those to follow, were given by the Respondents' Expert Witnesses. First up was the eminent chemist Professor Stephen Hanessian, who is on the faculties of the Universities of Montreal and California (Irvine). He was presented by Mr. Craig Smith of Fish & Richardson representing the Chinese manufacturers JK Sucralose. Professor Hanessian said his mission was to give "a brief retrospective of the chemistry of sucralose."

The Professor ran into some immediate problems. His diagrams were different from those used by Professor Crich, which prompted Judge Bullock to worry that — "your diagram is kind of turned a little bit from the previous—". This concern was defused by reassuring the Judge that we—"organic chemists—have certain perspective—we like to draw—but—you're looking at the same molecule—."

Professor Hanessian explained that the classical protocol for converting sugar-OH to sugar-Cl involved two separate steps. The first was to "activate" the OH which made it easier to install the Cl (Chloride).

But sucrose has eight-OH groups, and to obtain sucralose, three of the eight must be replaced by chlorine. But not just any three; three specific OHs. He framed the task by analogy to—"two cars in a train with preferred seats—so the challenge, then, is to have the chlorines—[which are passengers]—come in and occupy the preferred seats—[which are those]—with the best view—Perhaps they are not the easiest to get to—but access to them is possible."

Selecting three of the eight was nicely exemplified by this analogy. The three 'passengers' would certainly seek out the best seats, but how the selectivity could be enforced would take more than one tutorial. Nevertheless, Professor Hanessian continued:—"[n]ow, I had the good fortune many, many years ago to show the first application of the Vilsmeier reagent in the chlorination of a sugar derivative—[in a]— simplified procedure—[where]—activation and chlorination proceed at the same time in the same [vessel] sequentially".

The second Expert Witness for the Respondents was Professor David Baker, who was presented by Ms. Marcia Sundeen of Kenyon & Kenyon representing four Chinese manufacturers including Hebei Sukerui. Dr. Baker, a distinguished professor at the University of Tennessee, was responsible to teach Judge Bullock how chemists determine the structures of the compounds they make.

He explained that reactions in organic chemistry frequently give several products, and these must be separated. This mixture is "pumped through a column –[that is}—packed with small particles which interact—[with the mixture in such a way]—that the components—will travel through the column at different speeds—[and so]—emerge at the other end of the column—at different times".

With the components now separated, the task is to "prove" the structure of each, and so Dr. Baker described the various types of spectroscopic measurements commonly used in the chemistry laboratory to arrive at a satisfactory "proof."

However, this concept of proof is certainly not shared by everyone – least of all lawyers. My coach, Goutam Patnaik (Gooch), and I had several disagreements. If I wrote that "compound XYZ would definitely not be formed in this reaction," he would replace "definitely" with softer and more guarded "probably."

Upon further thought, that may not be such a bad idea. The certitude with which I used the word "definitely" is usually based on the fact that my instrument did not "see" compound XYZ – which really means, more precisely, that if any XYZ was formed, the amount was below the detection limit of my instrument. With the latter qualifier, should I have said that XYZ is not detected by use of the very best instrument avaible to me?

Alternatively, should I have said that I do not *think* XYZ is present? The problem is that if I adopted this rendition, I would leave open the possibility that XYZ had possibly been formed. But there was no supporting evidence for that possibility!

These different meanings of proof in chemistry *versus* the law would be one of the dilemmas confronting Judge Bullock.

After Dr. Baker, it was my turn. My tutorial on the chemistry of tin included how these compounds are named, and mindful of my *faux pas* at the pre-trial rehearsal, I was obsequious to Judge Bullock.

"Your Honor, I am here to talk about nomenclature, one of the most boring aspects of organic chemistry, I'm sorry to say.

"—But it's a necessary evil, especially if we are to go through the gauntlet of tin nomenclature in the '969 and '551 patents. First, the Latin word for tin is *stannum*, and so the symbol is Sn. Tin can —[combine with]— two atoms, as in tin dichloride, that is stannous chloride—[or with]— four chlorines as in tin tetrachloride, that is stannic chloride ."

I explained that there is "organic tin, for example where the tin is bonded to organic moieties— [as in DSDE which]— stands for distannoxane diester—".

The final tutorial was given by Dr. Eric Walters, a professor of biochemistry and molecular biology at the Rosalind Franklin University. Eric was the expert witness for the Chinese manufacturer, Niutang, which was also represented by Gary Hnath. So he and I saw a lot of one another, and since his expertise is in the phenomenon of sweetness, I was to learn a lot from him in our 2 weeks together.

With that:

JUDGE BULLOCK: Does that conclude the tutorial?

MR. HNATH: It does conclude Respondent's tutorial.

JUDGE BULOCK: Okay. Thank you. I feel like I've gone through a year of chemistry in about two or three hours. . ."

ONE year? More like 3 years of chemistry, your Honor – I felt like saying. But I thought better of it.

We then broke for lunch.

9.2 Exchange of Pleasantries and Unpleasantries Began

The afternoon session of the first day was devoted to technical legal maneuvering about what would or should not be allowed in the trial. The most visible lawyer in the room was Mr. Goulet of the Complainants' legal team. All morning long during the tutorials, he had been as–busy-as-a-bee, flitting from one cluster of lawyers to another, apparently trouble shooting, soothing hurts, or organizing this and that, but in any case being very visible, intense, earnest, and exuding angst.

He would soon have the full attention of the court, because the Complainants' lead attorney, Mr. Tom Jarvis, would introduce him to the judge.

JUDGE BULLOCK: Please be seated.

MR. JARVIS: Tom Jarvis, Tate & Lyle, I believe we have reached accommodation with Respondents on motions in limine *(these are motions that were made to the judge before the trial started)*, motions to strike relating to issues. I'll turn that over to Mr. Goulet to describe.

Mr. Goulet would now take center stage.

MR. GOULET: Good afternoon, Your Honor.

JUDGE BULLOCK: Good afternoon.

MR. GOULET: There are several of the motions that we've reached resolution on. Complainants moved. . . . .

JUDGE BULLOCK: Can you bring the mike a little closer, please?

MR. GOULET: Sorry Your Honor.

JUDGE BULLOCK: Thank you.

With the mike closer things would now heat up.

MR. GOULET: Complainants moved to preclude Respondents from making evidence or argument on issues for which they lack standing—The parties have agreed to withdraw those three motions.

JUDGE BULLOCK: Okay. If you could just tell me exactly what—they are.

"Absolutely" says Mr. Goulet with relish.

And he talked of this and that and so on so forth with the result:

JUDGE BULLOCK: So that one is resolved.

And after he talked some more about this and that:

JUDGE BULLOCK: Is that agreeable to—

With which the judge was cut short by "our" lawyer, who probably had heard enough and wanted to get on with it. . . . .

MR. HNATH: Yes, it is Your Honor, that's correct.

But Mr. Goulet would rise again.

JUDGE BULLOCK: — I am going to begin with Complainants' motions—to preclude Respondent's reliance on late produced documents—.

MR. GOULET: I think, Your Honor, we've partially resolved many of the issues. I think that the parties are now in agreement — However, one issue we'd like guidance from the Court on — is what will happen — [if]—Complainants *(i.e.* ***his*** *side)* produced a document late— [and as a result] — they're not permitted to rely on it. Respondents (*i.e.* ***our*** *side)* then choose—[to use]—that document in cross-examination of a witness.

In plain language, Mr. Goulet was recommending that if one side produced a piece of evidence after the deadline had passed, that side should not be allowed to use it; but the other side should, because one side should not be penalized for the other side's 'slackness' - to use his terminology.

Charges such as the latter provoked responses from just about all of the Respondents' lawyers. And Mr. Goulet's colleagues came to his defense. And so the judge ruled.

JUDGE BULLOCK: If it's out, it's out, would be my view.

From my seat in the court, I agreed with His Honor - if it's out for the goose, it's out for the gander; but that would not be the end of the matter for Mr. Goulet.

MR. GOULET:—And cannot be used during cross-examination? *(This was obviously not what he had hoped for).* The parties generally agree that it could be used during cross examination. The question is whether it would come into evidence if the opposing side opens the door.

JUDGE BULLOCK: Yeah. I don't know if that gets to your question—

So even the Judge is confused by Mr. Goulet's question. And so Mr. Goulet clarified:

MR. GOULET: Well, Your Honor, one point of clarity is — Complainants (i.e. **his** side) asked for documents from Respondents (i.e. **our** side) repeatedly — but — those documents were not produced until after discovery *(i.e. after the due date)*— but **we** — want to use them as evidence and should not be penalized because **they** chose not to produce them until after the close out discovery (**emphasis added).** So, I think the parties are in agreement that the party that produced a document late cannot use it, but the opposing party can and should not be penalized for the other party's slackness. (*Wow! He is not being nice).*

JUDGE BULLOCK: All right. If the parties agree that a document can be used regardless of it being filed late—[and]—there's no objection, then I have no objection.

MR. GOULET: Thank you, Your Honor.

But not so fast—Judge Bullock's "no objection" was met with an objection.

JUDGE BULLOCK: Did you have a comment, Sir?

This was addressed to Mr. Smith.

MR. SMITH: Yes, Your Honor. This is Craig Smith from Fish & Richardson— The proposal that we had discussed is that we wanted parity among the parties meaning if —[a document is produced late] — and it's out, we propose it not be used for any purpose whatsoever.

I thought that was what the judge meant when he said "If it's out, it's out—"

MR. SMITH:—My understanding —[is that]—if a document was produced late by one party, the other party could use it for purposes of cross-examination. My feeling is that, if it's used for cross-examination—it still doesn't come into evidence.

How can it NOT "come into evidence"? If the matter can be brought up by cross-examination, even though the document containing the evidence was filed late, what is the judge supposed to do? Can he say to himself "I must disregard what I just heard in the cross-examination, because it was filed late due to the other party's 'slackness' "?

Mr. Goulet obviously did not agree, and the battle between Mr. Goulet and Mr. Smith soon engulfs other lawyers, and of this back-and-forth there would be no end in sight. So finally:

JUDGE BULLOCK: — "I think you're saying it depends on who gets to use it. I think we're going to get ourselves tangled up in knots—if I don't draw a bright line on this one, so — I would encourage the parties to — work this out amongst yourselves and I will just leave it at that."

MR. GOULET: Yes, Your Honor. Thank you.

Whew! What a relief – if only momentary.

JUDGE BULLOCK: "Let's move on to the next one. Motion number 604079, Complainants' motion to preclude the testimony of Dr. Stephen Hanessian concerning validity— is now moot—because Dr. Hanessian will not be testifying regarding validity, is that correct?

This brings Mr. Barney to the floor. Mr. Barney is one of "their" lawyers and he is the only lawyer with an undergraduate degree in chemistry (from the Naval Academy) as I recall.

MR. BARNEY: Your Honor, this is James Barney on behalf of the Complainants. That *(i.e. what the Judge just said)* was the Respondents' response in **their** brief (emphasis added).

So clearly there is going to be a battle. In one corner is the Complainants represented by Mr. Barney. In the other corner is Ms. Hamilton from Fish & Richardson who represents J.K. Sucralose for whom Dr. Hannesian is engaged as an Expert Witness.

The quarrel centers around a maze of legal technicalities that was resplendent with phrases such as "prior art", "rebuttal witness statement", "infringement", "validity", "claim construction" etc. Why this one disqualifies that one, but supports the other went on for five transcript pages of back-and-forth lawyer-speak. The reason for the fight would only become clear during the cross-examination of Dr. Hanessian — on DAY SIX of the trial.

So, most of the afternoon was consumed by lawyers on both sides making sure that there would be no surprises. For example, that "they" did not produce any documents that "we" had not been allowed to read.

But there was an interesting problem which ***ostensibly*** *dealt with an expert who had failed to established his credentials by previously submitting an Expert Report. That would have been naughty – so much so that it brought "their" lead attorney to his feet.*

MR. JARVIS: Your Honor. This is Tom Jarvis, if I might add a response to this? The problem is that Respondents were using Chinese language documents with their experts, who can't read Chinese, don't understand it, but were giving testimony about those documents—[and this amounts to]—the attorney's argument being fed through their expert.

In other words "our" lawyers, who represent Chinese clients, don't read or speak Chinese, but they are spouting stuff as though it came from a Chinese expert. How shameful of "us"!

JUDGE BULLOCK: So you're saying that undercuts the credibility of the witness testifying, right?

MR. JARVIS: No, Your Honor, I don't believe it was witness testimony. They (*i.e. my lawyer colleagues*) testified they couldn't read it. <u>It's not their testimony at all. It's as if it's attorney argument.</u>

Let's not beat around the bush. The lawyers for the Respondents (only, of course) are telling their experts (like me) what to say, right?

JUDGE BULLOCK: So what you're saying—[is]— that the witness was, in effect, adopting attorney argument—doesn't that go to weight?

I knew it.

MR. JARVIS: I believe it obviously goes to weight, but I believe, Your Honor, it deprives Complainant of an opportunity to meaningfully cross-examine them, if they (*i.e. "our" Expert Witnesses)* know nothing more than what they were told by their attorneys………..

JUDGE BULLOCK: So the facts were the —[attorneys' and these]—came in at the (*Expert's*) deposition, is that the argument?

MR. JARVIS: Effectively, yes, Your Honor, because all their expert could do was to say I'm relying on the Chinese language document that I can't read, don't' understand, that's being fed to me by my lawyers or Respondents' lawyers.

JUDGE BULLOCK: Thank you. —Yes.

This was addressed to Mr. Patnaik, my tutor Gooch, who took umbrage.

MR. PATNAIK: That's not quite accurate. I think it would help if we reviewed some of the documents at issue—there were five exhibits that were relied on by Dr. Walters or Dr. Fraser-Reid (*i.e. me*) in their witness statements. I think it might help to look at some of those documents.

When all is said and done, the problem can be envisaged as follows: A Chinese scientist produces a report written in Chinese. A translator is employed who is not a scientist and so needs help with determining what the document says. A ready source of help is the lawyer who needs the thing translated. How convenient?

Unfortunately, how the wise judge ruled will have to be imagined, because the Court went into confidential session.

In Sect. 7.1, I stated that my Expert Report, Witness Statement, and Deposition were all prepared before the trial actually got started. However, I did not then realize that there are restrictions on how "the other side" could use (or misuse) them. So the arguments of our lead attorney, Mr. Hnath, to Judge Bullock were educational to me:

Mr. Hnath complained to the judge about "large portions of Dr Crich's ***witness statement"*** *being misused, and followed up with a veritable lecture on how the various documents could, and could not, be used.*

MR. HNATH: The principle is [that] **deposition testimony**—of experts is not admissible. It's not part of the record.

JUDGE BULLOCK: So you'd rather they (*the Complainants*) refer to the **witness statements,** is that—

MR. HNATH: The **witness statements**, yes (*i.e. they are admissible)* [but] **expert reports**—are not part of the record. Expert **deposition testimony** is (*also*) not part of the record, but —they *(i.e. Dr. Crich's lawyers)* just read him long passages from the Respondents' (*i.e. our*) expert **depositions** and say, do you agree with that?—That's just putting our **deposition testimony** right into the record—"

Recall that a ***Deposition*** *is taken by the lawyer to gather information, and it is not distributed to all lawyers. The* ***witness statement*** *is also taken by the lawyer; But the transcript is sent to lawyers on both sides before the trial.*

MR. GOULET": Your Honor, we believe that is appropriate—He *(i.e. Dr. Crich)* uses that **deposition testimony** to inform the Court of his own opinions—[the fact that]— they don't like what their—[own]—witnesses said in deposition, is no basis to preclude Dr. Crich from referring to that testimony, and stating whether he agrees or disagrees—

JUDGE BULLOCK: Why is it more appropriate though to refer—to their **witness statements**—[rather than to their] —**deposition** and **expert** reports?

MR. GOULET: Because they're inconsistent, Your Honor, they change their position and Dr. Crich is pointing it out, that's why they want it out of the record, Your Honor.

JUDGE BULLOCK: So your position is that you're quoting from the depositions and reports so as to challenge—the Respondents—?

MR. GOULET: That is correct, Your Honor.

Which brings forth and angry Mr. Hnath:

MR. HNATH. If they want to impeach our experts, they can cross-examine them on the stand.

JUDGE BULLOCK: Yeah. That's the normal way—so I'm going to deny the motion.

The afternoon's legal tussle dragged on; but finally, Mr. Goulet raised something that even I could understand.

MR. GOULET: — Your Honor—this is Paul Goulet— I'm sorry— over here.

The judge had been looking all around to find the speaker.

JUDGE BULLOCK: I'm sorry, I thought—I'm looking over here.

MR. GOULET: People don't often see me, Your Honor, I'm actually standing. . ."

The good-humored Mr. Goulet stands about 5 ft 6 in.

After three pages of lawyer-speak, Mr. Goulet finally gets to the point.

MR. GOULET: Your Honor, it might make sense to discuss allocation of trial time.....it's our understanding.... [that].....any cross-examination—[that]—Complainants undertake would be charged to Complainants, but we also believe that any cross- examination....[that]...the Staff attorney undertakes would be charged to the party who's proffering the witness.

*On this basis, instead of a separate amount of time being allotted to the Staff, the "**side**" that presented most witnesses would have to donate more of its time to the Staff. But the "Staff", who are independent lawyers (see Sect. 8.1), work for the International Trade Commission, and hence for the Judge. The* **"side"** *that presented most witnesses would undoubtedly be the four Respondents, each with its own team of lawyers.*

This forced the judge to seek clarification:

JUDGE BULLOCK: I'm sorry, Staff's would be—?

MR. GOULET: Charged to the party that is offering the witness; so for example if Mr. Paulraj cross-examines—

And so the judge interrupts:

JUDGE BULLOCK: Well, let me head that one off. I think the best way is to have Staff have its own allocation of time—

What a relief—albeit temporary, for Mr. Goulet would soon find something else to rail about; but this would be of interest to me.

This had to do with the participation in the trial of Dr. Juan Navia who is an employee of McNeil Specialty Chemicals where the formulation of Splenda was developed. In my view, Dr. Navia is one of the unheralded giants of the Splenda epic. He is the sole scientist named on Patent No: 4,950,746 as Inventor of a commercially feasible process for preparing sucrose-6-acetate by "blocking" one of the 8-OH groups of sucrose. Not only is position-6 the most reactive, but chlorination at this site depresses sweetness. Navia's "blocking" procedure was accomplished by using a tin-catalyst, and was so efficient that alternative routes to the product in question, sucrose-6-acetate (see Scheme 7.3), seemed inconceivable. The problem for our side was to show that the Chinese manufacturers were ***not*** *using the tin-catalyst procedure.*

Dr. Navia's participation in the trial was therefore logical; but there was a problem, as "our" lead attorney, Mr. Hnath, would now explain.

MR. HNATH: "Thank you, Your Honor — There's one witness, Juan Navia, who's an inventor on the 463 patent. Dr. Navia testified (*in some other capacity*) as a representative on behalf of the Complainants (*i.e. "them"*). Complainants listed Dr. Navia as one of their witnesses *for* ***this*** *trial*—[but]—they later said they're not going to call Dr. Navia as a live witness.—We don't think there's any reason to call Dr. Navia as a witness.—He's up in Philadelphia. We would like to use his testimony—*(not live, but by deposition—so as not to)* —use additional trial time.

Clearly, Mr. Hnath was deeply concerned about using "additional trial time"! But the busy-as-a-bee-lawyer would have none of that.

MR. GOULET: Your Honor, we've subpoenaed Dr. Navia. He has agreed to come to trial. Complainants believe that his live testimony would be beneficial to the Court, so —if they *(i.e. our side)* want to use him as an **adverse witness**, we would not agree to do so by deposition—.

JUDGE BULLOCK: Okay. But as I recall, the rule is that for a —deposition, the party can use that for any purpose.

MR. GOULET: That is correct, Your Honor—[but]—they late provided—[the request for]—Dr. Navia. At that point, we said—we believe his **adverse testimony** should come in live.

MR. HNATH: Your Honor, there's no rule that says we had to provide the request by—[a certain date]—

JUDGE BULLOCK: Yeah, —I've had— [some]—worked out any time during the trial—.

What seems to be the problem here?

The issue apparently is that Dr. Navia may produce, in Mr. Goulet's words, "adverse testimony", and if "our side" wanted to use him as an "adverse witness", they (i.e. Mr. Goulet et al.) would not agree to do so by deposition. They want Dr. Navia live and in person.

In other words, if Dr. Navia is going to shaft us, we want it done in public – not by deposition in a secluded place by Mr. Hnath (Oh No!).

This is not going his way, and so Mr. Goulet tries one more time to get a face-to-face with Dr Navia.

MR. GOULET: Your Honor, I believe that Dr. Navia is looking forward to testifying — He's been subpoenaed. We certainly plan to cross-examine him if he does come.

But the back-and-forth gets settled by Judge Bullock.

JUDGE BULLOCK: Well, —I think we'll just go with the — deposition designation—.

MR. HNATH: Thank you, Your Honor.

Judge Bullock then outlined certain aspects of decorum that would be observed in his courtroom.

9.3 The Judge's Rules – Fortunately I Don't Chew Gum

JUDGE BULLOCK:—bottled water is fine. —Any other beverages are prohibited, any food is prohibited, and this is one that comes up all the time, so I would ask counsel to please tell your staff, so I don't have to interrupt the hearing, not to chew gum during the hearing.

Fortunately, I do not chew gum.

JUDGE BULLOCK: Anything else? We finished right on time. Okay, let's hope we do the same with the trial. We recess for today and we'll start tomorrow at 9. Thank you.

Chapter 10
Day Two of the Trial

Yesterday, the exchange of pleasantries in the morning was followed by the exchange of unpleasantries in the afternoon. Today, the case began for real at 9:01 am on Thursday February 21, 2008.

10.1 Tate & Lyle's Lead Attorney Outlines What the Trial Is All About

JUDGE BULLOCK: On the record. Before we begin with opening statements, are there any preliminary matters that I need to deal with? If not, let's proceed with the opening statements.

MR. JARVIS: Good morning, Your Honor.

JUDGE BULLOCK: Good morning,

MR. JARVIS: "I'm Tom Jarvis from Finnegan, Henderson, Farabow, Garrett, & Dunner firm. We represent Tate & Lyle Sucralose, Inc., and Tate & Lyle Technology, Limited, Complainants in this investigation involving Certain Sucralose, Sweetener Containing sucralose, and Related Intermediate Compounds Thereof, Investigation Number 604.

"It's our pleasure this morning to provide you with our opening argument — to establish why there has been a violation of Section 337 *(Section 337 patent litigations deal broadly with foreign access to United States markets)* by an evolving network of Chinese manufacturers and distributors of sucralose and the network of infringement that can only be adequately solved by the remediate orders uniquely available from the ITC.

"Your Honor, sucralose is an amazing product. It is a zero calorie sweetener that has swept through the markets. Splenda is the trade name associated with sucralose. It's the best low calorie sweetener in the market, and I'd point out two reasons, the first **it's made from sugar and tastes like sugar** (emphasis added), and second,

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simply by inspecting those packages, you can readily observe that there's no warning label required by the FDA.

"You might compare that to other sweeteners—that do require warning labels and information panels. **It's made from sugar, it tastes like sugar** (emphasis added)..."

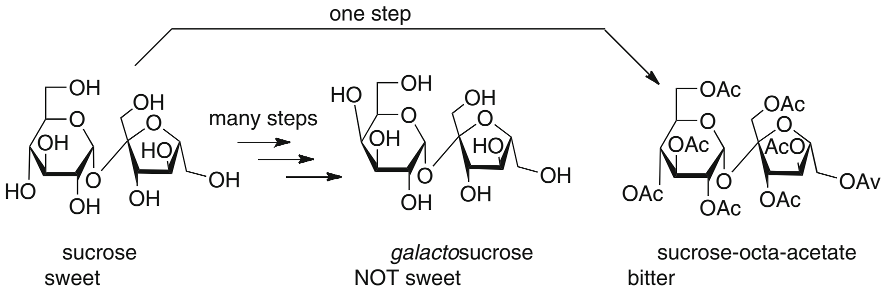
This aggrandizement of Splenda - "it's made from sugar, it tastes like sugar" - had been challenged by the makers of Equal – and the ensuing litigation ended in a settlement which, it is speculated, was favorable to Equal.

The manufacturers of Equal could have saved themselves millions of dollars in lawyer's fees if they had contacted me. As shown in Scheme 10.1, I would have taken sucrose, (which is sweet), and converted it to galactosucrose (which is not sweet) to prove that "it's made from sugar", but does NOT taste like sugar. And I would also have converted sucrose to sucrose-octacetate to show that "it's made from sugar", but it is BITTER.

Mr. Jarvis went on to explain that some hydroxyl bonds of sucrose were replaced with chlorine to create "a more stable molecule, a molecule so stable that the body — no longer recognized it for metabolism, but the taste receptors perceived a certain sweetness—".

MR. JARVIS: "Your Honor, with those two great advantages, you have a product which is a breakthrough pioneer type product in the market. Now, Splenda's the trade name we all know and love—a table top formulation, that is about less than one percent sucralose—[we]— sometimes call these high intensity sweeteners—and the United States is the premium worldwide market for high intensity sweeteners including sucralose. If the United States market is lost to improper foreign competition, then Splenda could easily go the same route as saccharin, which was lost to Asian competitors more than 20 years ago".

A condensed account of the discovery of sucralose in Professor Leslie Hough's lab at King's College, London, England was summarized, including the "legend" of how the post-doctoral fellow, Shashikant Phadnis, discovered that the compound was sweet. (The truth about this discovery is discussed fully in Sect. 4.1.5)



Scheme 10.1 These are made from sugar – but do NOT taste like sugar

MR. JARVIS: "Now, Your Honor, from those early days in the discovery of sucralose in 1976, almost 20 years passed before the necessary development, engineering of prototype plants and FDA approval could be obtained to sell the product in the United States. Now during that 20-year period, the patent protection for the underlying molecule began to lapse.

"But what has continued are the **manufacturing process patents** (emphasis added) that are at stake in this litigation. Now there have been two series of manufacturing processes, a first generation and a second generation. The first generation was initially operating in two separate plants—and the intermediate product was then shipped from Newport, Tennessee to Athens, Georgia where the [Johnson & Johnson] subsidiary —carried out the back end processing, packaged it, and made it available for sale—[*as Splenda*]—

"But the prospects for Splenda were so strong that over 100 million dollars was invested to create those two operating plants to make the first generation of Splenda. Simultaneously, research—was undertaken towards a second generation, more efficient method for manufacturing sucralose.

"And when that method was finalized, another 100 million dollars was invested to build a plant in McIntosh, Alabama. That facility was far more efficient. So—the first generation plant—was eventually closed.

"What drove that investment, writing off 100 million, investing another hundred million? Well the first witness this morning, Austin Maguire, will explain that, in order to be successful, —it was perceived that Splenda must compete in the very large volume beverage market, and the prime competitor for that market was aspartame (*the sweet ingredient in Equal*).

"So to become competitive and succeed in the overall market—management set a goal for the research and development people, –[requiring that they]— reduce the cost of manufacturing sucralose by 90 percent, so when—[they]—can produce it for 10 percent of the current cost, we'll open a second generation plant, and that is McIntosh.

"Your Honor, with that introduction I'd like to give you a quick video tour of the McIntosh facility."

Whereupon, a video of the gleaming facility at McIntosh, Alabama, completed in 2007, was shown.

MR. JARVIS: "Your Honor, the video tour was made during the expansion construction at McIntosh in excess of a hundred million dollars to expand that facility, and that process was completed in 2007—

"Your Honor, the McIntosh facility is located in a fairly rural area of Alabama; it's in Washington County — one of the poorest counties in Alabama, and as Mr. Maguire (*the CEO)* will testify, they employ a large number of people — and that gives a basis for our domestic industry claim.

"—some of the senior management are also located in Decatur, Illinois, and so their activity is accounted for in our domestic claims as well."

It was therefore clear, presumably, that Tate & Lyle was a good, corporate citizen, by putting its factory in" one of the poorest counties" so as to help the poor!

But the trial was not just about Chinese manufacturers. Respondents also included businesses that sold sucralose to beverage companies, makers of ketchup, toothpaste, lipstick etc. *Mr. Jarvis went on to describe that the "interlocking business relationships— are very difficult to decipher" between the various Chinese Respondents.*

Slides are shown that reveal "the combination of—manufacturing and distributor Respondents that are named in the investigation—"

MR. JARVIS: "Your Honor, the distributor Respondents are —scattered both in China and in the United States—[and]—the combination of the manufacturing and distributor Respondents named in the investigation— are operating both in China and the United States. However, — do not conclude that those are all. Those are all we could name in our Complaint, largely because of difficulties in identifying importations of their products. But — there are many sucralose manufacturers and distributors operating throughout China."

The testimony was interrupted, again, because the Court had to go into confidential session. As usual, this meant that the juicy parts of the exchanges are not reported in the public Court transcript, and so I am not at liberty to reveal them.

When the Court resumed a presentation was made by one of the Complainants' lawyers:

MR. FOSTER: Thank you, Your Honor. I just wanted to address one of the specific issues that was raised—with respect to the 463 patent, the 969 patent, and the 551 patent which, as you heard from our presentation—cover—processes used in the production of—sucralose—

Mr. Foster spent nine pages recounting litigation, going back to 1930, which dealt with "the importation of products made abroad in accordance with United States patent without consent of the patentee—", whereby a "foreign enterprise—[was]—taking jobs from American workers by doing off shore that which they could not lawfully do in the United States". I will spare readers the dreary recounting of the "Commission decisions", "exclusion order", "tariffs", "legislative history", "recent Kinik decision" and even a 1934 case about— oxides of iron suitable for pigment purposes,—but also then, 'any of the foregoing oxides calcined or burned or processed in any other manner—'. The legal connection between "oxides of iron" and the possibility of "some sort of nexus test" for the patent infringement case currently under litigation, was beyond the comprehension of this chemist. But I am sure the lawyers got it.

Mercifully it came to an end, and Judge Bullock, sensing the need, advised that "we take a break now".

Upon our return the first attorney for the Respondents to address the Judge came forward. She was Ms. Marcia Sundeen.

MS SUNDEEN: "I'm Marcia Sundeen, and I'm representing several of the Respondents in this investigation." (*See Sect. 8.1.)*

After outlining who her Clients were, she wasted no time in getting to the point.

MS. SUNDEEN: You— heard this morning that Complainants Tate & Lyle manufacture and sell sucralose. What you didn't hear is the hefty profits that they make on sucralose. And just so there is no danger of me saying any confidential information, I would like to go on the confidential record.

Darn it! These details are not in the public record of the trial, and readers will just have to imagine what was disclosed.

10.2 Tate & Lyle “Big Shots” Versus the Respondents’ Lawyers

The Court resumed after lunch, and got off to an encouraging start. The visible angst of yesterday’s busy-as-a-bee lawyer, Mr. Goulet, was soon on display again.

JUDGE BULLOCK: I believe there was a question—concerning when Mr. St. Laurent—was going to appear—[Is]—there a way we can make sure that he gets on today?

We later learned that there was an emergency that required Mr. St. Laurent to testify before the close of today’s session.

MR. GOULET: Your Honor, we’ve agreed, regardless of the state of the testimony today, Mr. St. Laurent can take the stand at 3:15 to ensure his cross [examination] is completed.

JUDGE BULLOCK: Regardless?

MR. GOULET: Correct.

JUDGE BULLOCK: Okay. That’s great. I, again, applaud your spirit of cooperation. One less thing I have to deal with.

Mr. Goulet’s head must have swollen massively.

MR. JARVIS: Tate & Lyle Sucralose, Tate & Lyle technology call, as their first witness, Austin Maguire.

Mr. Maguire, would you take the stand, please?

BY MR. JARVIS:

Q. Sir, could you state your name, please?

A. Austin Maguire.

Q. What is your position, sir?

A. President of Tate & Lyle Sucralose.

I was keen to see how this top gun from Tate & Lyle would handle cross-examination; but I had to wait. In Sect. 8.2 I noted that the “direct witness statement” should have been prepared BEFORE the trial started. There were some problems with his that required three pages of back-and-forth “lawyer-speak” about just ONE sentence, and this had to be fixed before the witness statement could be admitted into evidence. The cross-examination could then begin.

Q. Mr. Maguire, have you prepared a direct witness statement for this investigation?

A. I have.

Q. Sir, do you see it in front of you?

A. Yes

Q. Mr. Maguire, is that your testimony to questions posed to you by counsel?

A. Yes, it is.

Q. Sir, would you sign and date that witness statement, please?

A. There is one correction—reference CX- 512 should read CX-512C.

Q. Thank you sir. Are there any other corrections necessary?

A. No.

So the interesting part could now begin – or so I hoped! However, a new "can-of-worms" was about to be opened.

JUDGE BULLOCK: Excuse me, before we proceed—Is there any objection?

MR. O'CONNOR: "Just briefly, Your Honor—in order 50, you had previously ordered certain exhibits to be struck—and [also]—the **exhibit number.** (*emphasis added).*However, they have left in the **text** of the stricken exhibit in the witness' testimony—

Although this seemed to be a case where the "picture" was removed, but the "story" was not, Judge Bullock assured Mr. O'Connor:

JUDGE BULLOCK: —I set it up that way—so I think it is appropriate—

MR. O'CONNOR: I understand. Thank you, Your Honor.

But Mr. O'Connor had not finished; there was a more serious issue.

MR. O'CONNOR: In Mr. Maguire's direct witness statement—[he addressed]—trade dress issues with packaging. There is a separate trade dress issue pending in district court in Philadelphia between—my client and McNeil Specialty Products—*(which developed Splenda)*—so —there's no foundation for this witness to be testifying about litigation in Philadelphia to which Tate & Lyle is not a party".

Therefore Mr. O'Connor wants the pertinent pages deleted from Mr. Maguire's Witness Statement.

MR. GOULET: Your Honor, if you examine (*the question and answer*) you'll see that it nowhere references any litigation with Mr. O'Connor's client—it simply states that the products appear similar, and there are **trade dress** concerns—[but]—I fail to see any reference to – trade dress [litigation] in the question and answer.

Nevertheless, Mr. Goulet's boss, Mr. Jarvis is more generous.

MR. JARVIS: Your Honor, we're willing to strike that sentence. The importance of the similarities of the packaging is that it will be shown in subsequent testimony that the Respondents model their product, product packaging, — for purposes of ease in market entry, so once they are able to piggy back on to the trade recognition of the Splenda and Tate & Lyle products, that makes it very easy for them to move into the market and is one reason we seek an execution order.

JUDGE BULLOCK: All right. But you're agreeable to taking out the reference to the trade dress suit, is that correct?

MR. JARVIS: Yes, Your Honor, we're doing that right now.

JUDGE BULLOCK: All right—Does that resolve your—well, I'll let you speak.

MR. O'CONNOR: I still think I'm going to have to address the trade dress issues if they're going to make—[it]—part of their case—

The problem, to my untrained eye, is that the packaging/trade dress issues are different from manufacturing issues, and the lawyers for the packaging clients wanted to make sure that their packaging case did not become conflated with manufacturing patent infringement issues. Not surprisingly, lawyers for other *packaging clients had their say about this thorny issue. It took several pages of the transcript before it was sorted out.*

Cross-examination of Mr. Maguire by Gary Hnath (my boss), the lead attorney for the Chinese manufacturers, GDFII, then began.

MR. HNATH: Good afternoon Mr. Maguire.

A. Good afternoon.

Q. We met before in October for your deposition in Decatur, is that right?

A. That’s correct.

Q. —You were involved in the investigations that led to this ITC action, at least at a high level, is that correct?

A. I was involved at a management level, yes.

Q. And you authorized the filing of this —[lawsuit]—is that right?

A. Yes, I did.

Q. Did Complainants *(*i.e. *YOU)* make any effort to contact GDFII—to obtain information about their process for making sucralose before the—[lawsuit]—was filed?”

A. No, we did not.

The answer surprised me. How could Tate & Lyle have concluded that there was patent infringement, if they did not have any “direct information” about the procedure being used by the Chinese suspects? Aha! There was some “indirect information”—but for that to be divulged, the Court had to go into Confidential session – Sorry!

10.3 A One-Handed Economist – Never ‘On the One Hand, but On the Other’

The Open Session resumed in time for the promised 3.15 pm cross-examination of Mr. St. Laurent. He provided analytical services, and there were questions about how this was done; but nothing spectacular, to my mind, emerged. And so there was a brief break.

JUDGE BULLOCK: Back on the record. Let’s proceed with our next witness.

MR. GOULET: Good afternoon, Your Honor. Complainants call Dr. Marvin Hayenga to the stand.

Dr. Hayenga was “duly sworn”.

MR. GOULET: Good afternoon, Doctor. Could you state your full name for the record?

Dr. Marvin L. Hayenga is a retired economist from Iowa State University. He signs his witness statement and was ready to go.

But before we could hear from Dr. Hayenga, there was a mild confrontation between Mr. Goulet and Mr. Patnaik, (Gooch, my coach), over issues concerning certain exhibits that would “affect the foundation of Dr. Hayenga’s testimony.” This wrangling went on for four pages of the public transcript, and the interchange *became more and more dense to this poor chemist - especially when "invalidity and non-obviousness" minutiae were brought into the confrontation. Fortunately, at that point, Judge Bullock descended with finality.*

JUDGE BULLOCK: I am going to deny the Motion to Strike and allow this to remain in. Thank you.

Whereupon the busy-as-a-bee lawyer, Mr. Goulet, offered "Dr. Hayenga for admission as an expert in the field of economics of the food and agricultural sector including the sweetener industry—[and]—we make the witness available for cross examination."

The cross examining counsel, Mr. Goutam Patnaik, Gooch, as we called him and he called himself, was then an associate in the firm of Bingham McCutchen. Gooch had guided me through my various statements, and so I was anxious to see him in action.

BY MR. PATNAIK:

Q. Good afternoon, Dr. Hyenga.

A. Good afternoon, Mr. Patnaik.

Q. Dr. Hayenga, I understand—that you analyzed three things in your direct testimony—namely the business conditions in the sucralose market, the ease of access to the US markets by foreign competitors, and Tate & Lyle's investment in the domestic manufacture of sucralose, is that correct?

A. That is correct.

Q. And for this investigation, we're talking about allegedly infringing sucralose made in China, correct?

There were some differences between what Dr. Hayenga was saying in Court, and what he had said during his deposition by Mr. Patnaik some weeks earlier.

Q. —Why have you changed your mind?

A. Maybe because another interpretation occurred to me.

I was impressed at how adroitly Dr. Hayenga dealt with his change of mind. Gooch apparently wanted to broaden the field.

Q. Are you aware of any manufacturers of sucralose outside of the United States or China?

A. No, not for sure.

Q. I think, during your deposition you referred to some Indian manufacturers of sucralose.

A. Yes

Q. Tate & Lyle isn't alleging that any of those Indian sucralose manufacturers are infringing the patents asserted in this investigation, are they?

A. Not in terms of my reading of the complaint, no.

Q. And I think, during your deposition you testified that you believe that the Indian companies had figured a workaround the Tate & Lyle patents, do you recall that? *There was some hesitancy in the reply, so Gooch quoted from his deposition:*

Q: —I think you testified that you, I quote "I read an article that there's some Indian companies that thought they had figured a way to work around the Tate & Lyle patents that may get into production in the next year or two. I don't remember where I saw that, like Business Week or someplace like that, just a, you know, lay publication."

Q. You would agree that there is nothing improper about trying to work around or get around other company's patents, correct?

A. Oh, that's classic procedure by most food processing companies.

Q. And would you agree, Dr. Hayenga, that there is more than one way to make sucralose, wouldn't you?

A. Well, I am not a food scientist, but just based on the tutorial that I was exposed to the other day, I think the answer is, clearly yes.

Q. You would also agree that sucralose has been profitable for Tate & Lyle, correct?

A. Oh, definitely.

Whereupon the trial proceeded in confidential session – and that concluded the day's work.

Reading the trial transcript gives me the impression that Gooch's basic question to Hayenga was: Are there other manufacturers that have made sucralose? If the answer is yes, as with the Indian manufacturers, why aren't they being charged? Why have the four Chinese companies been selected for infringement claims by Tate & Lyle?

However, that somehow sounds to me like saying to the traffic policeman, "Sure, I was going 75 miles per hour, but so were all the drivers around me. How come you only gave me a ticket?"

Nevertheless, to my non-legal mind, this was an important cross-examination, because Gooch got Dr. Hayenga, one of Tate & Lyle's Expert Witnesses, to establish that it is possible to make sucralose by a procedure, other than that developed by Tate & Lyle. This declaration was necessary because, as we learned in Mr. Maguire's cross-examination, Tate & Lyle had not contacted our Chinese clients (GDFII) about their manufacturing procedure before filing the infringement lawsuit.

Chapter 11
Day Three of the Trial

Friday, February 22, 2008 – The day began at 9:03 am.

11.1 The Cross-Examinations Begin for Real

JUDGE BULLOCK: — I see you all braved the weather and made it in. Are there any preliminary matters before we resume?

(*There was a tremendous winter storm in Washington on Thursday night, and those of us who got to the Court, faced some major obstacles).*

Of course, the busy-as-a-bee lawyer, Mr. Goulet, for Complainants Tate & Lyle, was immediately on his feet to raise some "quick housekeeping issues."

MR. GOULET: A couple of quick housekeeping issues, Your Honor—The parties have met and have agreed as to the amount of time used by each party yesterday, and we'd like to put that on record. — We agree — [that we]— used one hour and 35 minutes, they used two hours and 50 minutes, and the Staff used 40 minutes.

Clearly, Mr. Goulet is disturbed that the distribution of time between "them and us" is so disproportionate. He makes it seem that we have been hogging the time. But does it matter that "they" have only one set of lawyers, whereas "we" have four sets?

Anyway the judge agrees that "we lost a little ground", but that does not mollify Mr. Goulet.

MR. GOULET: —my next housekeeping matter–is due to some scheduling issues, we're changing our order of witnesses—

JUDGE BULLOCK: Okay—that's fine—

Needless to say this caused a ripple effect. The lawyers for the Respondents had naturally planned the sequence of their cross-examinations, and that would have to be tossed out because of the new scheduling. Ms. Sundeen was the first to complain.

MS. SUNDEEN: Your Honor, I would like to make one comment on Mr. Goulet's comments on the schedule. We were just informed today about

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_11,

Complainants' change of plan—[but]–we've prepared today for Dr. Crich—[and]–we would reserve the right to—come up twice, and not necessarily conclude all of Dr. Crich's cross-examination at one time.

MR. GOULET: I understand the nature of their position, Your Honor, that's not a problem with Complainants—

Whereupon Judge Bullock said, ***actually said****, "Whatever!" - just like an exasperated teenager; and he went on to explain that because of "hearing-room space" we had to finish a week from today. He did not add 'so let that be a warning to you'; but the message was loud and clear.*

11.2 So You Think You Can Be An Expert?

JUDGE BULLOCK: Back on the record—

MR. JARVIS: Tom Jarvis for Complainant Tate & Lyle—[there are]—some partial agreements, partial disagreements–much of Dr. Ware's testimony deals with chain of custody—He received a sample of some sucralose and transferred that sample to a testing laboratory. Some of the exhibits (i.e. *data*) were stricken. However Dr. Ware is capable and has personal knowledge of testifying that he received the sample and sent it to the testing lab—So in our view, Your Honor, Dr. Ware, a Ph.D. analytical chemist is fully capable, from his personal knowledge, of identifying the test review.

Actually, the "fully capable" man's name is Dr. Ware Flora–so he should have been addressed as Dr. Flora, not Dr. Ware.

MR. JARVIS: My recommendation–is that given Mr. [Flora's] family situation, his need to catch a flight today, is that we allow him to testify on the exhibit as it exists and if we're not able to reach full agreement–we could meet and confer over the lunch break and argue it–that's my recommendation, Your Honor.

Not surprisingly, this "recommendation" does not sit well with "our" side.

MR. HNATH: "I think that's problematic, Your Honor, and while we want to cooperate with the witness and his circumstances, we don't know what to cross-examine him on if we don't know what in his witness statement is in or out.

"There are some documents that are referenced in the witness statement which have been stricken altogether, and they're still in the witness statement".

"—there are documents in his testimony where he says, very specifically,—[that]–this person provided me this sample on this date, and I sent it on this date to the testing lab.

"—In other cases, they've taken out the document, but they've left in the testimony.

"We think that's contrary to Your Honor's order that said, if the document comes out, the witness can't rely on it.

MR. JARVIS: "Your Honor, we're happy for Dr. Ware to be cross-examined on any and all of this.

"I'm sorry I said Dr. Ware, that's his first name. It's Dr. Flora. Much of this is in his personal knowledge, a Ph.D. Chemist in analytical chemistry who works in the sucralose business every day of his life. I think it would be —reliable testimony. We can move forward".

The problem was that some documents, concerning lab test results on analyses of tin, had arrived after the cut-off date, December 3, 2007. That date had been set by the Judge, to ensure that the experts of the Respondents ("we") would have time to scrutinize the test results. "We" would then include appropriate comments about the analyses in "our" own expert witness statements, prior to the court hearing.

However, although the stricken, late-arriving documents themselves had not been admitted because of late arrival, some of the **results** *therein had found their way into Dr. Flora's witness statement - for which the December 3rd deadline did not apply. Naughty! Naughty?*

Needless to say, this led to substantial back-and-forth between the two lead lawyers Jarvis and Hnath. This lessened the chances that Dr. Flora would be able to get away early:

JUDGE BULLOCK: How long do you anticipate–cross-examining this witness?

MR. HNATH: It was going to be 45 minutes—[but]– it will now probably be an hour and a half because I've got to cross examine him on the stricken documents. I mean to preserve my rights now, I have to assume it's in.

That was not all:

MR. HNATH: I feel we're being disadvantaged because we accommodated Complainants' counsel by taking the witness out of order–but we were surprised that–testimony relating to stricken documents–were still in it.

The prospect of the cross examination taking a longer time, did not cause Judge Bullock to leap from his chair with joy! Indeed his Honor indicated that come hell or high water, the trial **had** *to be completed in a week's time, February 29th.*

But Mr. Hnath continued:

MR. HNATH: There are test results that are embedded in these documents, test results that were not disclosed to us until after December 3rd, and so that is another reason why the underlying testimony should not come in."

Mr. Hnath posed a hypothetical:

MR. HNATH: There are some issues, for example, if Dr. Flora says I tested the sample and I got this result for tin, if the document was produced to us after December 3rd, and the testimony is now coming in, that's a test result that was disclosed to us after December 3rd.— So even if the document is out and the testimony is in, it is still a late-produced test result — and we don't think that should come in through the back door through testimony because late is late."

Now, on the first day, Mr. Goulet had said "the opposing party–should not be penalized for the other party's **slackness***". He probably never thought that this caustic edict could now be applied to his party.*

Several lawyers for the Respondents joined in, and supported Mr. Hnath. Ms. Hamilton of the firm of Fish & Richardson, representing one of the other Chinese manufacturers (JK Sucralose) pointed out that:

MS. HAMILTON:–in Order 48,–you said Complainants may not rely on any test results that were produced after December 3, 2007– and so I just wanted to make sure that however we handle this witness, given—[the]– special circumstances about his need to leave today, that we don't traverse this order, which is an order we relied on in drafting our witness statements—

And then Ms. Hamilton took off her kid gloves:

MS. HAMILTON:— the reason you issued the order was because – after December 3rd, we didn't have sufficient time – for our experts to consider it when drafting their rebuttal expert reports —. So to – allow them to say 'I remember the test results by personal knowledge so –I can leave it in my witness statement', really runs afoul of this, and it's going to be a problem for several witnesses, and I think it's going to keep recurring–And I think the easiest thing is to rely on the strict ruling that you gave here and apply it uniformly from this point on.

Mr. O'Connor also jumped in—feet first. He represented clients who are not manufacturers, but purchase sucralose from distributors.

MR. O'CONNOR: — my concern is that **Dr. Flora, who did not submit an expert report, is going to be allowed to give expert testimony** essentially against people that are not going to be able to defend themselves, and then —later in the case – they are going to try to use that against my clients.

So even if you have won the Nobel Prize, you cannot testify as an expert if you have not submitted an expert report?

Mr. Paulraj also jumped in.

MR. PAULRAJ: —As Complainants have already stated earlier, Staff is obviously entitled to challenge the sufficiency of evidence presented against the –non-participating Respondents—[and so]–the Staff would have an objection to— the Complainants disregarding –[the Judge's orders]—

If only life could be easy! The "nonparticipating" Respondents are the distributors, and salespersons of various types. How are they affected – since the trial is supposedly about manufacture infringement? Also, if Dr. Flora did not submit an expert report prior to the trial, so that his credentials could be vetted, he cannot be used as an expert in the trial. So what exactly was Mr. Jarvis hinting at by stating that Dr. Flora is a "Ph.D. analytical chemist"?

MR. O'CONNOR: In terms of Mr. Jarvis' statement—I do want to make sure it's clear—[that]–the stipulation–does not include my client–since my client is not a manufacturer–[but buys product]–from distributors, my concern is that Dr. Flora, who did not submit an expert witness report, is going to be allowed to give expert testimony essentially against people that are not going to be able to defend themselves–

Anyway I was confused by all of this, and I was not the only one. At one point:

JUDGE BULLOCK: Just a moment. Let me make sure I understand. There are several things going on here. Let me try to understand one thing, is —one of the issues –-whether or not it was appropriate for this witness to testify because he was not an expert–[or are you]– withdrawing that?

Mr. Hnath surprised me:

MR. HNATH: We are withdrawing that".

JUDGE BULLOCK: What about the other Respondents?

Well Mr. O'Connor was NOT withdrawing. He "STOOD" on the objection!

MR. O'CONNOR: I stand on that objection, Your Honor".

Nor Mr. Zhao:

MR. ZHAO: MTC Respondents have the same concerns.

The distributor Respondents' lawyers remained firmly against admitting Dr. Flora's scientific evidence, whereas the Respondents' lawyers for the manufacturer had been reluctantly persuaded.

But Mr. Jarvis was not about to take this apparent challenge to Dr. Flora's expertise lying down – so to speak.

MR. JARVIS: I believe the Federal Rules provide that one with specialized knowledge by virtue of their experience and occupation may give information and testimony to that specialized knowledge. *(And to think that I wasted time submitting an expert report!)* They need not be admitted as a testifying opinion expert, and so I believe we've fully briefed that issue, Your Honor.

Things were getting more and more murky, and so the Judge Bullock did what judges do – he made a ruling:

JUDGE BULLOCK: —I was hoping that, through negotiations—[the]—issue would go away, it hasn't, so I'll go ahead and rule on it— This is a close call, so what I'm going to do is deny the motion to strike the testimony based on the fact that he was not properly qualified as an expert witness —. Now the question then becomes whether or not I should reconsider the ruling I made concerning the witness testifying about tests that came in late — let's go off the record for a minute.

After the minute, Judge Bullock concluded that — "any reference in the testimony to studies that were late filed should be struck –"

The hassle surrounding Dr. Flora's upcoming testimony was all because of tin. If the presence of tin was detected in the factories of the Chinese manufacturers, that would be evidence, albeit very indirect and fragile, that the Chinese manufacturers were using tin, and therefore (probably?) infringing Tate & Lyle's patents.

But, as we shall see, detecting "the presence of tin" is not so simple.

So there was further hassle and then:

11.3 Was Tin Detected?

MS. Rosetti: Thank you, Your Honor. At this time, we would make Dr. Flora available for cross examination.

JUDGE BULLOCK: Thank you.

MR. HNATH: May I proceed?

JUDGE BULLOCK: Please.

MR. HNATH: Thank you.

BY MR. HNATH:

Q. Good morning, Dr. Flora.

A. Good morning.

Q. In your witness statement, you discussed tests by — University of Southern Mississippi?

A. Yes.

Q. Okay. And those were tests for tin?

A. USM did perform tests for tin, yes.

Q. What was the detection limit for that testing?

A. As I did not run the tests at USM, I won't speak on their behalf, but it is my understanding that the detection limit can vary from analysis-to-analysis–My understanding of the technology is that that would be in the—low part per billion, perhaps one part per billion or, even the part per trillion range for tin.

Q. Do you know of the specific detection limits that would correspond to any of the specific test results that you discussed in your witness statement?

A. I do not have those numbers readily available —

Q. Can you tell me, with respect to particular test results—what detection limits would apply?

A. Again, I believe there is a document that does provide these details from USM.

Q. But apart from what you have read in documents, could you tell me out of your own personal knowledge, what specific detection limits would relate to the specific test results in your witness statement?

A. Is there a certain sample you are referring to?

Q. Dr. Flora, my question was, apart from what you read in documents, do you have independent knowledge of what detection limits were used for a specific test that are discussed in your witness statement?

A. I would say – question again please? Either you or the court reporter.

Q. Yes. Apart from what you read from documents, do you have any personal knowledge as to the detection limits that would apply to specific test results in your witness statement?

A. My primary source for that information would be exchanges from USM, and I do recall—I think you'll find [that] it doesn't vary by much from sample-to-sample and that it's in the low part per billion range.

Q. Have you ever been to the University of Southern Mississippi to observe the tin testing?

A. No, I have not.

Q. Did you participate personally in any of the tin testing that the University of Southern Mississippi did?

A. No, I did not. I understand they are a very reputable source for such analyses, so I did not see the need to.

Q. Do you know what standards they use for their tin testing?

A. I do not know the specific standard they used, but it is my understanding that they use commercially available standards.

Q. Do you know specifically where they got those standards?

A. I do not know the specific origin that they used. It may be referenced in their method protocol, but I can't recall the specific source—

Q. Dr. Flora, I wonder if you could please answer my questions. Your counsel will have an opportunity to follow up. Okay? Do you know whether any controls were used or not by the University of Southern Mississippi?

My Goodness! I would not want to be cross-examined by Mr. Hnath (my lead counsel). He is making Dr. Flora seem like nothing more than a messenger. It makes me think of the thousands of times that I have accepted the analyses of my students without checking the original data for myself.

A. Yes, I believe they did control charting and I believe that's indicated in their methodology.

Q. ICPMS just detects total tin, is that right?

ICPMS stands for Inductively Coupled Plasma Mass Spectrometry. Ordinary day-to-day mass spectrometry is a procedure that allows rapid detection of components in a sample. It is commonly used for urine samples of athletes suspected of using performance-enhancing drugs. The ICP mode allows testing of trace elements to very sensitive levels e.g. parts per trillion

A. ICPMS detects total tin. That is correct.

Q. And does it allow you to distinguish between organic tin and inorganic tin?

A. If one takes a sample and analyzes –[it]–the result provides– a total analysis for tin, however, it does not distinguish between organic tin or—it does give an analysis for total tin —

Whatever that means!—but Mr. Hnath is not satisfied.

Q. It does not distinguish between organic tin and inorganic tin, is that correct?

A. To be clear, I could envision an experiment where one could do that, but it is my understanding that the way that it has been utilized is a measurement for total tin.

The judge does not fall for this obfuscation either.

JUDGE BULLOCK: So it doesn't distinguish?

THE WITNESS: It does not distinguish.

JUDGE BULLOCK: Between the two?

THE WITNESS: In the way that it was run.

JUDGE BULLOCK: Okay. Mr. Hnath.

BY MR. HNATH:

Q. Did you ask University of Southern Mississippi to do an experiment to distinguish between organic and inorganic tin in their testing?

A. No, I don't recall that.

Q. Does Tate & Lyle have ICPMS capabilities?

A. Tate & Lyle has —

But the witness' response was promptly interrupted by Mr. Jarvis.

MR. JARVIS: Your Honor, that's going to require confidential record.

Darn it! We always miss the juicy parts.

JUDGE BULLOCK: On the confidential record.

So whether or not Tate & Lyle have ICPMS facilities that specifically distinguish between organic and inorganic tin remains a mystery to the public.

The open session resumed in the afternoon after lunch with a new witness for the Complainants. Mr. Fues (who had taken my deposition) presented Dr. Robert Walkup, one of the Inventors of the crucial 463 patent.

In the Preamble (Chap. 8, Fig. 8.1), I discussed the case of a reaction involving three components, A, B and C, and showed that ***the sequence of addition is important to the notion of an "in situ" process.*** *This could now apply to three components in the 463 patent, namely sucrose-6-acetate, thionyl chloride and DMF (which also serves as the solvent).*

The issue was seen by me as one of the "Swords of Damocles" that hung over the trial, and loosening of this sword now fell to Ms. Sundeen. She would cross-examine Dr. Walkup who is the first-named Inventor of the 463 patent, which I regard as the "lynch pin" of the trial (see Sect. 7.4). Dr. Walkup is now a minister in the Presbyterian Church (see Sect. 9.1).

11.4 The "*In Situ*" Sword of Damocles

BY MS. SUNDEEN:

Q. Good afternoon, Dr. Walkup.

A. Good Afternoon.

Q. My name is Marcia Sundeen.—I represent Respondent Sukerui–You're an inventor of the 463 patent, right?

A. That is correct.

Q. And in connection with the invention—my understanding is you conducted quite a few experiments—correct?

A. Of course, yes—

Q. Could you look in your cross-examination notebook–do you recognize that as one of you lab notebooks?

A. Yes, I do–

Q. And in connection you examined various variables–one those variables [being] different acid chlorides. Correct?

A. Multiple acid chlorides, multiple types of reaction conditions, multiple configurations of vessels, yes. Many different variables.

Q. Besides conducting different experiments, —one of the variables you looked at was the order of addition of the different reagents, right?

A. That is correct.

Q. And were you the one that came up with the idea of adding an acid chloride to a mixture of sucrose-6-acetate and DMF, rather than forming a Vilsmeier reagent first and then adding the Vilsmeier reagent to — sucrose-6- acetate–?

A. Certainly, there were several other inventors on this. I believe I may have conducted the first experiments that are documented.

Q. But was it your standard reaction conditions to add the acid chloride to the mixture of DMF and sucrose-6-[acetate]?

A dispute followed, that required Ms. Sundeen to challenge Dr. Walkup with what he had said at his deposition. He finally had to agree with her:

A. That was my standard procedure–

Whereupon the trail proceeded in confidential session–that lasted most of the rest of the day.

Chapter 12
Day Four of the Trial

Monday, February 25, 2008—court began at 9:04 a.m.

12.1 We Will Have to Get Out of Bed Earlier

Before Mr. Goulet can get in "a quick housekeeping matter", the Judge has one of his own.

JUDGE BULLOCK: Back on the record. I understand that the parties—are requesting that—I expand the trial day by 20 minutes to a half an hour—I need that hour at lunch, so—that gives us an hour and a half over what we have.

MR. GOULET: That should work very well, Your Honor. Thank you.

JUDGE BULLOCK: Okay—keep thinking about other ways you can cut this down—Anything else, other preliminary matters?

Mr. Goulet had some, of course.

MR. GOULET: Just a quick housekeeping matter—we're happy to say that we've resolved nearly all —and we'll work together to provide Your Honor with a list of all standing expert witness statements that need to be moved into evidence —".

JUDGE BULLOCK: That's good news. I congratulate the parties on their hard work—let's proceed with our next witness.

12.2 Now I Ask You! Would Such Hospitable People Infringe?

MS. ROSCETTI: Complainants call Dr. Fan Wu to the stand.

BY MS. ROSCETTI:

Q. Good morning, Doctor.

A. Good morning.

There was the usual verification of the witness statement and then:

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_12,

MS. Roscetti: —And finally, we make Dr. Wu available for cross—examination

BY MR. HNATH:

Q. Good morning, Dr. Wu.

A. Good morning.

Q. And I'll be relatively brief this morning. We've met several times during the inspections. My name is Gary Hnath. Nice to see you again.

A. Nice to see you.

Dr. Wu was a member of the Tate & Lyle team that had conducted the inspection of four Chinese manufacturers, one of which was the Guangdong Food Industry Institute (GDFII) factory in Guangzhou where I had met him (see Sect. 7.8).

The first few minutes of Gary's cross examination were carefully designed to establish that Chinese manufacturers were great hosts, all heart, no ill feeling whatever towards Tate & Lyle, which was planning to obliterate them.

Q. Let me first talk to you about the Niutang inspection. You actually attended two Niutang inspections, is that right?

A. That's correct.

Q. And the—[Chinese manufacturers] —were courteous to Tate & Lyle's inspection team, weren't they?

A. They were polite.

Q. And they also cooperated with the inspection?

A. They did.

Q. They sent a driver to your hotel to show you where their factory was located, is that right?

A. Correct.

Q. And they offered to provide you food, is that right?

A. I think we had our own lunch at that time.

Q. But they did offer, didn't they?

A. I don't recall.

Q. They made a room available for Tate & Lyle's inspection team?

A. Yes.

Q. And the room had running water and electricity?

A. Yes.

Wow! Water and electricity? But did you have to sit on the floor?

Q. Okay. And I think they put food and candies in the room for the Tate & Lyle inspection team, is that right?

Food AND candies? Too much!

A. Yes.

Q. And they provided extension cords?

A. Yeah.

Q. And they also stored samples in the refrigerator so they could keep cool while you were doing your inspection, is that right?

A. Yeah, —.

Q. They also provided food, didn't they?

A. Yes they did.

Q. They even provided Kentucky Fried Chicken, didn't they?

A. I remember that, yes.

Q. And when the Tate & Lyle team thought the Kentucky Fried Chicken didn't taste like home, they went out and got McDonald's, didn't they?

A. That is the case I believe.

Now I ask you –would such hospitable people commit patent infringement?

Q. And also — the samples were taken at all times of the night, isn't that right?

A. There were some late night sample points, yeah.

Q. And some between midnight and 6 a.m.?

A. I believe so.

Q. And the GDFII workers helped take the samples?

A. Yes.

Did the workers realize that they might be digging their own graves?

And so the cross—examination had led gradually to the samples that had been collected during Tate & Lyle's inspection of the GDFII manufacturers.

Q. And with the high temperature chlorination sample, they actually had to set up special connections in order to take that sample, is that right?

A. I believe some plumbings had to be modified in order for the samples to be taken.

Q. And you took swab samples during the GDFII inspection, is that right?

A. Yes we did.

Q. And GDFII also helped fill out the paperwork for World Courier, is that right?

A. Yes.

What!

Q. And they provided material safety data sheets to assist with the shipping of the samples?

A. I believe so.

What again!

Q. Even though the swab samples weren't on the list originally, isn't that correct?

A. I don't have any knowledge as to if the samples were on the list originally.

Q. And GDFII also helped fill out the paperwork for World Courier, is that right?

A. Yes.

Q. And while Tate & Lyle inspection team was waiting for —[the]—high—temperature chlorination sample, they provided stools and bottled water to make people comfortable, is that right?

A. Yes, that's correct.

Couldn't they also have provided a sauna?

Q. And during the GDFII inspection, did you do an IR (*infra red*) spectrum analysis of the mixture of thionyl chloride and DMF?

A. I believe I have conducted the IR collection of a sample that is a mixture of DMF and thionyl chloride.

Inspection of this sample would show which reagent, ***A*** *or* ***B*** *(see Scheme 7.4), had been formed.*

Q. And do you recall the results of that test?

A. I was only instructed to collect the IR data. I was not instructed to analyze the data.

Q. Who did you provide the data to?

A. I provided the IR data at the end of all inspections to Tate & Lyle's counsel.

12.3 Handling of Samples from the Inspection

Cross—examination of Dr. Wu by Mr. Hnath continues.

BY MR. HNATH:

Q. Now after the inspections, the samples were shipped to the United States and analyzed at CIBA, is that right?

Ciba Geigy was, originally, one of Switzerland's giant chemistry Institutions, and the initials stood for "Chemische Industrie Basel". It is not known whether the CIBA in Mr. Wu's testimony is in any way related to an "off—shoot" of Ciba Geigy.

A. Yes, that is correct.

Q. And did you have any role in the actual testing of the samples?

A. My role—was to compile the analytical data, then report—[them]—to Tate & Lyle counsel.

Q. So you did not do any of the actual testing, is that correct?

A. That is correct. I didn't do any testing—

Q. And was the separations group at Ciba involved in the testing of the samples?

A. To the best of my knowledge, yeah.

Q. Are you a part of the separations group at Ciba?

A. No, I am not.

Q. Have you ever operated an HPL machine?

A. I haven't operated any HPLCs at Ciba, but I did a lot of HPLC work at my graduate school.

The letters stand for High Pressure Liquid Chromatography. It refers to a method used by chemists to isolate components of a mixture. The method was described by Dr. Baker in his tutorial on Day ONE of the trial (Chap. 9).

Q. And you spoke to Dr. Crich—[*Tate & Lyle's expert witness*]—before the expert reports were submitted in this case, is that right?

A. That is correct.

Q. And did you discuss any specific test results with Dr. Crich in your conversation?

A. To the best of my knowledge, my conversation—was on general levels—

So, we learned that Dr. Wu works at CIBA; but a series of questions by Mr. Hnath revealed that he did not actually carry out any of the analyses, and only compiled the information and passed it on to Tate & Lyle's counsel, who apparently passed it on to their chemistry expert, Dr. David Crich (who was to testify soon).

The above questions made the harried Dr. Wu appear to be little more than a messenger – and the ***coup de grãce*** *was yet to come.*

Q: In fact, you don't supervise anyone who performed the tests and experiments that were performed in connection with this investigation, is that correct?

A: That is correct.

So both of these experts for the Complainants, Dr. Flora yesterday, and Dr. Wu today, have been made to seem like "paper pushers" who played no vital roles in the matters under litigation.

After this, the Court went off the record, so I cannot report on what was said about the test results. However, I can say that they were certainly important because they related to the presence of tin in the samples that were taken.

12.4 Analyzing Samples from the Inspection

When the session went back on the record, there was more discussion of the 463 patent. Yesterday, Ms. Sundeen's cross—examination of Dr. Walkup raised some issues concerning the patent. There would be lots more today with Dr. David Crich on the witness stand.

JUDGE BULLOCK: Back on the record. Please call your next witness.

MR. BARNEY: Your Honor, at this time, Complainants Call Dr. David Crich.

Professor David Crich, the chemistry expert witness for Tate & Lyle, is a very well—known, highly respected and innovative chemist, who has recently been appointed Director of the famed Research Institute at Gif—sur—Yvette, France.

12.4.1 Mr. Barney Presents Dr. Crich to Mr. Smith

BY MR. BARNEY:

Q. Good morning, Dr. Crich.

A. Good morning.

Q. Sir, in front of you, you should have a number of exhibits—

These "exhibits" included documents like "direct witness statement", "Supplemental direct witness statement", "rebuttal witness statement", and verifying these took two pages of the trial transcript, and then Mr. Barney offered Dr. Crich for cross—examination

MR. BARNEY: Your Honor, my co—counsel has informed me that Dr. Crich is not close enough to the microphone. I just wanted to remind him to speak up.

Mr. Craig Smith of the Boston firm Fish Richardson representing the Chinese manufacturer J.K. Sucralose was the first to cross—examine Dr. Crich.

BY MR. SMITH:

Q. Good morning, Dr. Crich.

A. Good morning.

Q. Dr. Crich, there are several witness statements that you have discussed just a moment ago. I'm going to primarily discuss two of them today. The first is your initial witness statement, and the second one was your supplemental witness statement, all right?

A. That's fine.

(Whereupon, the trial proceeded in confidential session.)

OPEN SESSION RESUMES

BY MR. SMITH:

As I outlined in the Preamble (Chap. 8), one of the problems facing the 463 patent (see Scheme 7.3), was that ***product #3*** *was formed at 85 degrees. Thus, position 1', the* *least* *reactive of the three OH groups of sucrose—6—acetate, had been chlorinated before the 2nd most reactive site, position 4. This really should not have been a big deal, for such vagaries happen in the lab all the time; but Dr. Crich cannot say this without inadvertently admitting that there are anomalies in the patent. Indeed his task is to make the case that the presence of* ***product#3*** *is "to—be—expected".*

So Mr. Smith gets to the point immediately.

Q: So you can't say whether or not the 4—position will begin to be chlorinated before 1' position will begin to chlorinate?

A: The activation energy for chlorination at the 4—position is lower—that means that chlorination will proceed more rapidly than at the 1' position. It says nothing about the **temperature** at which that chlorination will begin

Q: Dr. Crich, you do not know the temperature at which the 1'—6'—dichloro sucrose—6—ester [**product #3** in Scheme 7.3] would form, is that right?

Experiments could certainly have been done to provide the answers to this question; but the 463 patent gives no indication that such experiments were done—and this is not surprising since ***product #3*** *in Scheme 7.3, was not of interest, being only an intermediate on the way to what was actually needed,* ***product #4,*** *and thence to sucralose.*

A simple answer might be "We assume that ***product #3*** *is formed at 85 degrees." But that would definitely not have been accepted by lawyerly types such as Mr. Smith.*

So, Dr. Crich has to find some other way to affirm the presence of compound ***product #3****, and he resorts to logic!*

A: As I've already explained, the patent says that chlorination at the 1'—position takes place at a hundred degrees, and the rule of thumb that —is used by experts—[says that]— if you lower the temperature by 10 degrees, the reaction rate will be halved — [and so]—it's definitely happening at 80 and 85 degrees, just more slowly—And then we have the Khan paper — that explicitly says that chlorination at the 1' position happens at 85 degrees."

But Mr. Smith was well prepared.

Q: The Khan paper does not say that you get —**product #3**— at 85 degrees, does it?

A: I agree, but it does isolate molecules that have been chlorinated at the 1' position, so it says chlorination happens at 85 degrees at the 1' position.

Q: You cannot quantify how much [**product #3**] will occur at or below 85 degrees, is that right?

A: I’m not in a position to quantify, but I am in a position to say that it happens.

The lawyer versus *chemist confrontation would continue with the cross examination of Dr. Crich by Mr. Paulraj from the ITC Staff.*

12.5 Should 463 Have Been Rejected Because of “Obviousness”?

Mr. Paulraj’s cross—examination began in the confidential session, and then resumed in open session.

BY MR. PAULRAJ:

Q: So you agree with me, at least, that this paragraph of the patent teaches that you need to heat it up to some temperature before chlorination occurs at certain positions of the sucrose—6—acetate molecule?

A: Well, what one would understand—as an appropriate temperature—[at which] chlorination proceeds at a significant rate —.

But that was not good enough for Mr. Paulraj.

Q: Well— [the patent]— doesn’t say that chlorination proceeds at the sufficient or any **amount** of rate (emphasis added). It just says heating to an appropriate temperature in order to have this displacement occur. It doesn’t say that displacement occurs to any significant amount, does it?

*What is this question aimed at? After all we know that in going from sucrose—6—acetete → **product #4** (Scheme 7.3) chlorine must have replaced OH in “significant (or sufficient) amounts” since at—the—end—of—the—day Tate & Lyle ended up with sucralose.*

Q: Do you acknowledge, Doctor, that the patent takes advantage of these relative orders of reactivities (i.e. *6’ greater than 4 greater than 1’)* in order to make sucralose—?

A: I do.

Q: And the reason they’re able to use —[sucrose—6—acetate]— is because of the fact that there is this relative order of reactivities, isn’t that right?

A: That’s correct.

And here is where, in my view, lawyer Paulraj becomes very tricky, laying the foundation for the soon—to—come challenge.

Q: So in other words if — some other position than you mention — were somehow more reactive, this invention wouldn’t work, would it?

A: Not to form sucralose, I agree.

Q: So it’s your testimony, Doctor, whenever you have chlorination at the 6’ position [of sucrose—6—acetate] you’re also going to have a smaller proportion of molecules that are chlorinated at the 4 position and then even smaller amount chlorinated at the 1’ position.

A: Yes, that’s my position.

Q. Are there going to be any temperatures or concentrations where there's going to be no chlorination whatsoever of the 1' position?

A. Yes, absolute zero—

Q. How about room temperature?

A. How about room temperature? It will depend on concentration—.

Q. Now you don't have any experimental data to indicate at what **temperature** the 1'position will begin to chlorinate, do you, Doctor?

A. Well,——that's concentration dependent, so it's sort of a very broad question, but, no, I don't.

Mr. Paulraj goes back to the 463 patent, which raises the issue of "obviousness":

Q. If we go back to the first column of the 463 patent,—it cites—an article by Dr. Leslie Hough describing the order of reactivity, is that right?

A. That's correct.

Q. And here, they're chlorinating the sucrose molecule, not the sucrose—6—acetate molecule, right?

A. That's correct

The next series of questions arise from an article that had been published by Professor Leslie Hough (in whose lab the sweetness of chlorinated sugars was discovered, see Sect. 5.1.2). That work is summarized in Scheme 4.1 and has to do with the formation of the ***tetra****chloroderivative, which was named* ***"serendipitose"****. Paulraj's questions imply that the principles that enabled Hough to obtain the* ***tetra****chlorinated* ***"serendipitose"*** *from sucrose, would also have predicted that the* ***tri****chlorinated* ***product #4*** *would be obtained from sucrose—6—acetate (Scheme 12.1).*

Q. But the same principles apply with regards to chlorination of the sucrose—6—acetate molecule, isn't that right?

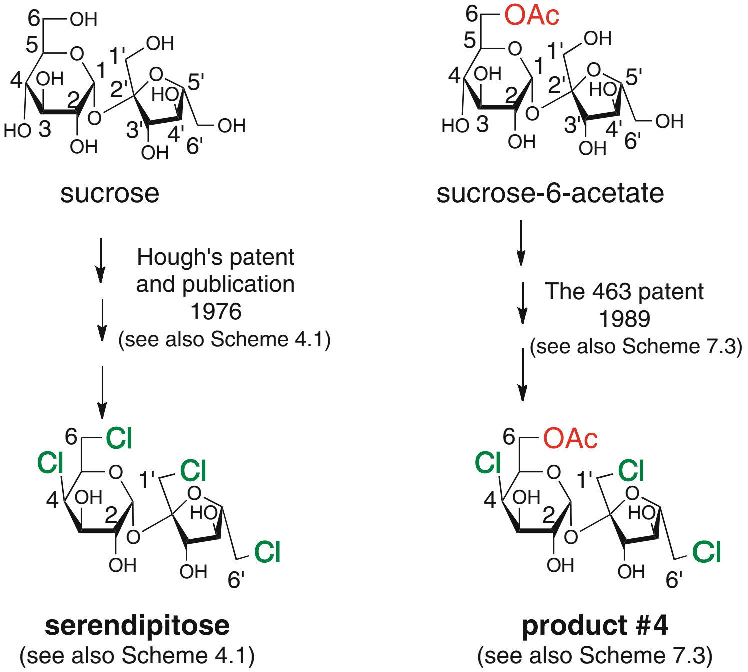
A. That's correct. All that's happening is [that] the sucrose—6—acetate —[removes]— the 6 position from the equation (i.e. *consideration).* **There is no reason to think that changes in the relative reactivity of the other positions** (emphasis added) would occur.

Q: And so if we applied the same general concept — a mild chlorination would give you—[the monochloroderivative **product #1**]—and a more vigorous chlorination would give you —[dichloroderivative **product #2**]— and an even more vigorous chlorination will give you the trichloride **product #4**, isn't that right?

A: That's correct.

The answer "That's correct" could place the 463 patent in jeopardy, for it now could be said that in light of Hough's conversion of sucrose to tetrachloride ***"serendipitose"****, (Scheme 12.1) it would have been "obvious to someone skilled in the art" that sucrose—6—acetate would similarly be converted to the trichloro analog* ***product #4.***

If light of such "obviousness" the patent for 463 should NOT have been issued in the first place — and so cannot now be subject to an infringement claim. Could the 463 patent be eviscerated on the basis of "obviousness"?



Scheme 12.1 "Obviousness" – Hough versus the 463 patent

A comment on OBVIOUSNESS (see also Sect. 7.2): The concept of obviousness is troubling. Probably it may be applicable to patents for certain types of invention, but for organic chemistry in general, and carbohydrate chemistry in particular, the concept may not be valid, as the following example suggests.

*At some point during the synthetic assembly of a complex molecule, an organic chemist will run into an unexpected obstacle. Circumventing this will require that a new approach will have to be developed. Rather than using the **real** substrate for testing out potential "new" approaches, the chemist will instead experiment with a simple, readily available **model.** However, in spite of all this extra planning and effort, the success rate for extending the findings from the **model** to the **real** case at hand is low. This is simply because the **real** substrates, by virtue of being more complex than the **model**, will have "appendages" here or there that interfere with the reaction. The concept of "obviousness" does not always hold.*

But Mr. Paulraj does not let up.

How could the 1' position be chlorinated at such a low temperature of 85 degrees? Doesn't chlorination at that position require much higher temperatures?:

Q: So we can turn to the language in the patent that—states that "The 1'—position is actually unreactive". That's how it characterizes the 1' position, doesn't it?

A: Yes, but it's all relative—that doesn't mean that it is not reactive at all. It's all relative—

Q: Agreed, Doctor. But it requires relatively severe conditions —[resulting in]— dark degradation products and tars, do you see that?

A. I do, but it's a discussion of the prior art.

Q. So when they're talking about 'relatively severe conditions' here, the only conditions that they're talking about is the temperature of the reaction vessel, isn't it?

A. No, that's not correct.

Q. The patent doesn't talk about achieving chlorination of the 1'position— other than by increasing the temperature—does it?

A. Well, it's talking about severe conditions—

Q. Let's talk a little about the activation energy required to chlorinate the different positions of a sucrose—6—acetate molecule.

A. Yes.

Q. Do you agree with me that, after the O—alkylformiminium chloride adducts (*e.g.* ***KEY COMPLEX****, Scheme 7.4)* are formed, you'll also need a certain amount of activation energy —in order to chlorinate those positions?

A. Oh, absolutely. Every chemical reaction has an activation energy—otherwise— if there wasn't an activation energy to react with oxygen, we would be gone, poof.

Q. I agree, Doctor, we don't want that to happen, but —do you recall—stating that "As a rule, the rate of reaction doubles for every—10 degrees Celsius increase in temperature—", do you recall that?

A. I do.

Q. But you don't know at what point the rate will start increasing, do you, at the 1' position?

A. Well, it will start increasing right from the beginning—[but]—it's—such a slow reaction that —doubling— makes little difference —

Q. Is it possible for some reactions **not** (*emphasis added*) to start occurring because there's not enough activation energy at room temperature, Doctor?

A. Well, the higher the activation [energy] the slower the reaction.

This difficulty in chlorinating the 1' position now causes Mr. Paulraj to visit Dr. Crich's witness statement, in which the complex concepts of activation energy, and the Maxwell—Boltzman distribution in chemical reactions are discussed. After several transcript pages about "the X and Y axes", "a finite number of molecules", "astronomical number of molecules", a curve that "never touches the X axis [because it] extends to infinity", or "to a point where it'll reach zero" Mr. Paulraj brings us back to earth:

Q: If we're talking about a real life system, as opposed to theoretical distribution there will be a point where there won't be any molecules that will have sufficient energy along the X axis if we keep going, isn't that right?

A. There'll be a point at which it's not detectable, I agree.

Q. There will be **no** (*emphasis added*) molecules at one point?

Dr. Crich does NOT fall for the trick question.

A. I said it's **asymptotic**, so it never actually comes to the X axis (i.e. *where it would be zero).*

JUDGE BULLOCK: Excuse me, sir, Let’s take our afternoon break, and come back at 3:30.

Whew! Thank you Judge Bullock. We all needed a break. Although questioning of the witness continued when court resumed, there seemed to be no justification for formation of ***product #3*** *in Scheme 7.3.*

Upon resumption, Mr. Paulraj pesters Dr. Crich about “activation energy” issues which, to my mind, are designed to show that ***product #3*** *(where position 1’ is chlorinated but position 4 is not) is unlikely. To further challenge Dr. Crich, Mr. Paulraj digs up a paper by Khan/Jenner about a pentaester analog (see structure* ***F****, Scheme 4.1) which contains some troubling precedents for the 463 patent.*

Q. Let’s put up the Khan paper—Now, the Khan paper talks about the formation of a (*compound that resembles* ***product #4****)* at 85 degrees, isn’t that right, Doctor?

A. yes—that establishes [that] a reaction can take place at 85 degrees at the 1’ position using the Vilsmeier chemistry.

Q. And now, right below that paragraph, you see several different examples of chlorinated sucrose derivatives that Khan identifies, you see that, right?

A. I do.

Q. At your deposition, Doctor, you couldn’t identify a single example in the Khan article— in which the 1’ and 6’ positions were chlorinated, but not the 4 position, isn’t that right?

A. I agree, but then I don’t think that I ever said there was one—

Q. Now you’ve stated, Doctor, that the pentaester route *(see Khan route in Scheme 4.1)* is **totally different** from the [sucrose—6—acetate] route that’s disclosed in the ‘463 patent, haven’t you?

A. I’ve stated [that] the pentaester route is different—but I don’t see that that changes the relative rates of chlorination of the three positions that are in question.

Mr. Paulraj actually returns to the comparison in Scheme 12.1 which had been discussed earlier.

Q. But you did state that it was totally different from using the [sucrose—6—acetate] route, didn’t you?

A. It is totally different in terms of the vigor that you can apply to the chlorinations.

Now comes the moment that every witness fears:

Q. Let’s look at your rebuttal witness statement—question 46—you state that, “Jenner (*and Khan)* uses the pentaester route, whereas the 463 patent uses the [sucrose—6—acetate] route. Those approaches to trichlorinated sucrose at the 4,1’ and 6’ positions are totally different.” Do you see that?

A. I do.

Q. And yet, you seem to be relying upon that pentaester route for your theory—You can’t tell whether that activation energy required to chlorinate the 1’ position of a pentaester is the same as—required to chlorinate the 1’position of [sucrose—6—acetate], can you?

A. No—[but]—the—relative values would be similar.

Q. Touch on a slightly different topic for a little bit, Doctor. Now, in your witness statement—

Mr. Paulraj opens a totally new line of cross—examination but I cannot report upon it, because:

The trial proceeded in confidential session

Were there other reasons for delegitimizing the 463 patent? We would have to wait until the next afternoon to find out.

Chapter 13
Day Five of the Trial

Tuesday, February 26, 2008

13.1 Semantics Indeed!

The morning of the fourth day of the trial was devoted to issues other than the 463 patent, and being confidential, the Court went into confidential session immediately.

The open session resumed by mid-afternoon. Ms. Marcia Sundeen of Washington's Kenyon & Kenyon law firm was ready to "offer Dr. Baker for cross-examination". Professor David Baker, a distinguished chemist at the University of Tennessee, was an expert witness for the Chinese manufacturers Hebei Sukerui.

After the usual certification of his witness statement, Dr. Baker was ready to face Mr. James Barney of Finnegan, Henderson. Earlier in the trial, Mr. Barney had cross-examined a number of the witnesses, and he came across as very formidable. However, on this day he adopted a most avuncular approach – to start with.

BY MR. BARNEY:

Q. Good afternoon, Dr. Baker.

A. Good afternoon.

Q. We met briefly at Dr. Crich's deposition last month. My name is James Barney.

A. Yes.

Q. It's good to see you again. I'd like to start today with the Mufti reference. You're familiar with that reference?

Recall that in (Sect. 7.4.2), the Mufti/Khan patent was seen a Sword of Damocles that hung over the trial.

A. Yes.

Q. Now, in your direct witness statement, you said that the Mufti patent discloses or suggests all of the elements of Claims 1 through 3 and 16 through 18 of the 463 patent, did I get that right.

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_13,

A. Yes.

Q. —Now, first of all you understand that the Mufti patent was cited to the patent office during prosecution of the 463 patent?

A. Yes.

In other words, the patent office had been made aware of the Mufti/Khan patent when they agreed to issue the 463. For this non-legal scholar, there is a problem. If the patent office allowed the 463 to be issued, how can it be subsequently invalidated? Can a patent be "recalled" like a governor or judge?

Q. And it's actually discussed at some length in the specification of the 463 patent?

A. Yes.

Q. So you'll agree with me that the inventors on the 463 patent were certainly familiar with the Mufti reference, being that they discussed it in their patent?

A. Yes, yes.

Q. So you'll agree with me that the Mufti patent discloses a monoester route to chlorination?

A. Yes.

Please revisit Scheme 7.4 to follow the upcoming discussions.

Q. And you do agree that in the preferred [strategy] of the Mufti patent the—[reagents are combined to give a]—**salt which is isolated and crystallized before being used in the subsequent chlorination reaction, correct?**

A. Yes.

Q. All right. Now you agree that's not what's claimed in the 463 patent?

A. Well, my view of the Mufti patent is that it's run more or less along the lines of the **classical Vilsmeier reaction** (emphasis added) as it was developed some 40 years ago—

Q. —I am correct that Vilsmeier reagent is a term that applies to a family of reagents?

A. Yes. —The Vilsmeier reagent is the chloroforminium species. That's the classical Vilsmeier—

Q. Just to be clear, the 463 patent—specifically require[s] a chloroforminium chloride salt, correct?

A. Yes

Q. And that's one type of Vilsmeier reagent?

A. The Vilsmeier reagent, in my mind, is the **chloroforminium salt** that's referred to in the patent**. *It's a thing of semantics*** *(emphasis added)*—

Mr. Barney explodes.

Q. **Well, it may be semantics, but it is important to this case** *(emphasis added).*

A. Okay.

Q. So let's make sure we get this straight. There have been reagents discussed in the last few days that various people referred to as Vilsmeier reagents.. **That does not necessarily mean those are chloroforminium chloride salts, does it?**

This made me appreciate the good lawyering of our lead counsel, Mr. Hnath. In Sect. 7.5, I noted that he had restricted mention of the term Vilsmeier to its usage in *the 463 patent claims. He clearly anticipated that "they" would seize on different usages.*

Q.—So in the Mufti patent, one of the things it says is that "The reagents may be formed in situ, but are preferably prepared in advance and isolated before being used".

A. Yes.

Q. And you understand the parties here disagree about what the term "in situ" means in that sentence?

A. Yes.

Q. Okay—one of the possibilities—, according to the words "in situ" is that the acid chloride is added to a mixture of DMF and sucrose acetate, is that correct?

A. I believe there was an example.

Q. Let me see if this helps—.

Whereupon Mr. Barney puts a "demonstrative" (diagram) on the screen.

Q. —I want to see if this matches your understanding of what Mufti discloses with respect to how you testified in your witness statement.

(Now, remember that the witness statement is prepared by the expert before the trial begins. In it the expert gives his assessment of the merits, pro and con, of the issues that will come before the judge).

Ms. Sundeen is quickly on her feet:

MS. SUNDEEN: Your Honor we have an objection to this demonstrative. I object to the title "Dr. Baker's understanding of Mufti."

MR. BARNEY: Your honor, it's a demonstrative.

MS. SUNDEEN: That's not necessarily what this is. That's Complainant's *[i.e. Tate & Lyle's]* characterization of this demonstrative. It is not a demonstrative that we prepared.

But Mr. Barney is all innocence at Ms. Sundeen's thinly disguised insinuation that Dr. Baker's "understanding" of the Mufti patent has not been faithfully reproduced.

MR. BARNEY: Your Honor, this is a cross-examination, and I'm going to elicit testimony from Dr. Baker that will either confirm or [will be rejected], and that the record will reflect it.

Judge Bullock ruminates for a moment, and then:

JUDGE BULLOCK:—Subject to that, I'll allow the cross-examination.

But Ms. Sundeen will not sit down.

MS. SUNDEEN: I have another objection. I don't believe we've been provided a copy of this—We provided our demonstratives to Complainants.—

The Court has to go off-the-record AGAIN to settle this – and His Honor makes a ruling, and so Mr. Barney continues.

BY MR. BARNEY:

Q. Your expert report is also in your binder.

A. Yeah.

Q. My question is does–[this language]—accurately reflect your understanding of the **in situ** embodiment—when you opined —that Mufti **discloses or suggests all the elements of the claims** [of the 463 patent] (emphasis added).

A. Yes it does.

Q. —In your response—you say—“Mufti’s use of the term ‘in situ’ is significant. In my opinion, this means that all of the reagents—can be mixed together in one pot and reacted”. Do you see that, sir?

A. Yes

Mr. Barney now gets to his point.

Q. —And you do understand, sir, that Dr. Hanessian, JK Sucralose’s expert, disagrees with you that this is disclosed in the Mufti patent?

A. I don’t believe that I have connected the two.

Q. Let’s take a look at his deposition transcript—Dr. Hanessian was asked:

“But in terms of this requirement that you add the acid chloride to a preformed mixture of both the sucrose-6-acetate a the tertiary amide, can you show me specifically where that’s taught in Mufti?

“ANSWER: As I said, Mufti does it in a different way. He prepares his Vilsmeier reagent in the flask and adds the sucrose acetates to that.

“QUESTION: Are those the same thing, or is there a difference?

“ANSWER: It’s a different process”

Q. Do you agree with Dr. Hanessian’s testimony there, Dr. Baker?

A. Well,—Dr. Hanessian does not go along with my finding that Mufti describes an **in situ** process—

Q. And you do understand that Dr. Hanessian has been one of the Respondents’ experts?

A. Yes.

So Mr. Barney has succeeded in driving a wedge between Drs. Baker and Hanessian who are experts for “our side”, Hebei Sukerui and JK Sucralose respectively. The document which Mr. Barney used to construct his wedge, was Dr. Hanessian’s deposition, which had been taken some weeks before by – Mr. Barney.

By eliciting an opinion from Dr. Hanessian that could be used against Dr. Baker, Mr. Barney had done a fine job. Our lawyers, Paitnik and Hnath, who had attended Mr. Barney’s deposition of Dr. Hanessian, had returned greatly concerned because they were sure that the Hanessian contrarian opinion on the Mufti “in situ” issue would provide the wedge that Mr. Barney was now using, so cleverly, to divide the Respondents’ experts.

And predictably, Mr. Barney would drive the wedge further in:

Q. So let’s look at step A (of the Mufti patent). Do you agree that Mufti discloses adding at least seven molar equivalents of an acid chloride—?”

I gasped when I heard the question, because it was a trick question. The words “seven molar equivalents” do NOT appear in the Mufti patent—they are ONLY in the allegedly infringed 463 patent. I hoped that David would keep his head.

A. I do not believe that Mufti addresses molar equivalents specifically.

What a relief!! David did not fall into the trap that had been so cleverly laid—and Mr. Barney strikes back by returning to the basic issue:

BY MR. BARNEY:

Q. Okay. Do you believe that that's the difference between the Mufti patent and the 463 patent?

A. Could I see the whole Mufti patent, please?

Q. You did study the Mufti patent though, right?

A. Yes

Q. And you realize that this is a very important case for all the parties in this room?

A. Yes.

Q. And you don't recall, off the top of your head whether it satisfies that particular limitation?

Mr. Barney might just as well have said to Dr. Baker: 'What kind of expert are you if your memory is so short'? Anyway "we" think Dr. Baker was a great expert because he did not fall into Mr. Barney's trap.

Q. Let's go down to the next limitation—Now it's your opinion that Mufti disclosed the formation of a —[Vilsmeier salt]— in the presence of a sucrose-6-acetate, correct?

A. Inasmuch as we assume that it goes through the Vilsmeier process, then you would expect a —[Vilsmeier salt]—to be involved in the Mufti process, yes.

Mr. Barney returns to the main problem:

Q. Okay. Sir you opined in this case that the Mufti patent discloses every limitation of Claim 1 of the 463 patent, correct?

A. You're quoting from where?

Q. Let me take a step back. You submitted an initial expert report in this case, correct, sir?

A. Yes.

Q. And in that report, you carefully considered all the opinions that you set forth in that report, correct?

A. Yes.

Q. Because you understand this is a very important case for the parties in this room?

A. Yes.

Q. And did you strive to provide a complete and accurate explanation of all your opinions in that report?

A. I did.

Q. Did you hold anything back?

A. Hold anything back, could you clarify?

Q. Did you intentionally withhold part of your opinions that would otherwise have been relevant?

A. No, but as the case progressed, we've discovered and uncovered and thought about processes in-depth—or I have, and the words may get modified some.

13.2 Proof: Law *Versus* Chemistry

Aggressive grilling followed on fine details of Mufti, the nature of direct and indirect proof – not a very auspicious ground on which to engage a lawyer. In my view, direct proof for the presence of the "salt" (Scheme 7.4) require making it, then holding it in your hand. Indirect proof would be to isolate products that could only have come from reactions of the salt with components of the reaction mixture. When Mr. Barney is unable to shake Dr. Baker's confidence he gets somewhat testy.

BY MR. BARNEY:

Q. Well, in your initial expert report—you set forth your understanding of the claim, correct sir?

A. Yes.

Q. And at that time, you believed those constructions to be the correct interpretations of the claims?

A. Yes.

Q. And again you didn't hold anything back—purposely?

A. No.

Dr. Baker must have been searching his brain to think of what could have said that could have been "purposely" misleading.

With use of the word "purposely", Mr. Barney cleverly sets another trap. This involves the difference between direct and indirect proof, as it is understood in science. Is salt ***B*** *(Scheme 7.4) formed in the "in situ" experiment described in the Mufti patent? What is the proof of its formation?*

Q. Sir, — you wrote your initial expert report—that –[the Mufti patent]—**required** the formation of the [adduct **B**] *(Scheme 7.4)* didn't you?

A. Yes.

Q. You didn't do any analytical research to support your opinion—did you?

A. No.

Q. But it's your opinion that it's inherently disclosed?

A. —as he describes the Vilsmeier process.

Q. Sir, how come you didn't say anything about this direct proof issue in your initial expert report?

A. Direct proof would be by spectroscopy or—some chemical means. An indirect proof would be a supposition or a rationalization—

Q. But if indirect proof can be used—then you believe that the salt **B** is in fact formed in that **in situ** Mufti process, is that correct?

This is another trick question. Recall that the 463 patent describes formation of salt ***B*** *explicitly; but the Mufti* ***in situ*** *experiment does NOT—although to chemists, it's formation is implicit - or the sucrose-6-acetate would not have been chlorinated. So does the Mufti patent really anticipate the 463 <u>if salt</u>* ***<u>B</u>*** *<u>was NOT "explicitly" formed?</u>*

The confusion and Mr. Barney's relentless pursuit causes Dr. Baker to become incoherent as can be seen from this answer:

A. If you can't show the chloroformiminium, but the Mufti process, the preferred embodiment that we were talking about here is a preformed Vilsmeier, and that does meet the chloroforiminim part, but the other reaction is conducted in a different way.

And the relentless Mr. Barney seizes upon Dr. Baker's apparent anxiety.

Q. Are you now changing your answer to question 53 to say the Mufti does **not** disclose formation of a —[salt]—under any circumstances—?

A. As I said—

Q. But you've also said—are you changing your opinion now?

A. No.

Q. And when you gave the testimony that it's a given that the—adduct **B** is a necessary intermediate, did you have a firm scientific basis for that testimony?

A. From my knowledge of the Vilsmeier reaction, yes.

Q. When you came to the conclusion that it's a given that the—[adduct **B**]—is a necessary intermediate, you didn't do any of your own analytical testing to prove that, did you?

A. No

Q. But you considered your knowledge and the literature sufficient evidence to make that statement under oath?

If Dr. Baker had been "thin-skinned", he may have construed this question as a challenge to his competence as an expert witness. But he kept his cool and answered appropriately:

A. Yes, based on the literature of the Vilsmeier reactions.

Q. —So I just want—to summarize what we have here—direct evidence—[are]—things like spectroscopy, visual observation, chromatography, correct?

A. Yes.

Q. And then we have another type of evidence, which you've called indirect evidence—[that]—would include things like supposition, rationalization. The relevant literature, and your knowledge of chemistry?

This brings Ms. Sundeen to her feet again:

Your Honor, an objection. That's an incomplete characterization of the witness' testimony—.

Mr. Barney: He can correct it, or she can correct it on her redirect, your Honor.

Judge Bullock overrules the objection, and Mr. Barney is soon showing that there are inconsistencies between what Dr. Baker wrote in his expert witness statement, and what he said subsequently at his deposition. The quotations confirm these inconsistencies.

Mr. Barney tries a softer approach, since harassing Dr. Baker has been futile.

Q. But in general —it's not improper to draw conclusions based on indirect evidence, is it?

A. In my own case, I much prefer to have data that back up what I –rationalize—

Q. But— you yourself have drawn conclusions—based on indirect evidence, haven't you sir?

A.—yes.

And here comes the soft squeeze to patch up the rift with Dr. Hanessian:

Q. —And certainly, you wouldn't criticize another expert for doing the same thing?

A. I wouldn't criticize him. I might argue with him about certain points.

13.3 Was the 463 Patent "Anticipated"?

But with direct versus indirect evidence out of the way are there other ways that the Mufti patent anticipates the 463 patent?

Mr. Barney returns to what Dr. Baker had said in his deposition and his witness statement and finds another "inconsistency" relating to what products are formed in the Mufti versus 463 patents.

Q. In response to question 58—you say—"Mufti does not disclose forming a reaction mixture of **product #1, product #2 and product #3** (Scheme 7.3)—do you see that?

A. Yes.

Q. Now, that is directly contrary to what you said in your expert report—isn't it sir?

A. Yes.

Q. Okay. So you're changing what you said at your deposition?

A. In regard to these chlorinated species.

Q. And what occurred between the time of your deposition and the time of your witness statement that made you change your mind that **product #3** would not form below 85 degrees?

A. Those chlorinated species would not form below that –[temperature]—And—what timeframe are we talking about here?

Q. Well, I believe your deposition was in January, so what changed between January and February that caused you to change your mind…?

A. And what made me change my mind?

Q Yes, sir.

A. I don't recall exactly.

Q. Was it discussions with attorneys?

WOW!!! Would that be so bad? Is it forbidden to check with your attorney if what you said in your deposition was okay?

A. It's something about—Tate & Lyle's **position** that, in order to prove infringement it is **not** necessary to have **direct** proof (*emphases added*), that each of these three compounds (*i.e.* ***products #1, #2 & #3***) is actually —present.

*Does Tate & Lyle's "**position**" mean that it does not matter whether **product #3** is present after all? Nevertheless, Mr. Barney returns to the testimony of his key witness, Dr. Crich, in the search of "proof" that **product #3** is definitely present. And he begins with a rather condescending question:*

Q. Let's talk a little bit about reaction kinetics. You're familiar with that, aren't you sir?

A. Yes.

Q. Okay. Now the reactions we're talking about in the 463 patent are kinetic processes, correct?

A. Yes.

A "kinetic process" may be regarded as a relatively unstable state of affairs. For example, you are drinking coffee, and the cup slips. You catch it in your lap. That could be considered a "kinetic process", because it is safe; but relatively unstable. Thus if you jump to your feet, the cup falls on the carpet. That is now a stable state of affairs. Falling to the floor is therefore a "thermodynamic process".

Q. And certainly you don't have any dispute that the Maxwell Boltzman is a well-established law in chemistry?

A. It's a basis for collision theory for reactions—from which we derive chemical kinetics.

Q. Okay. Now, you'll also agree that as a rule, the rate of reaction doubles for every 10 degrees increase in the temperature–?

A. That— [is]— a pretty rough and dirty estimate—but more or less.

Q. So you've used this rule of thumb?

A. Organic chemists generally do.

Q. And you were explaining here that—a reaction that occurs half as fast, will take twice as long to complete, correct?

A. Assuming all other factors the same.

Q. You could have a reaction that could take a very long time—because it occurs at such a slow rate?

A. Correct.

Q. Sort of like what Dr. Crich was talking about yesterday—

A. Some longer than others.

Q. Okay. And just to button this up—if you have a reaction that's occurring—at 85 degrees, and it is producing—species X—you would expect that same reaction to occur at approximately one-fourth the rate at 65 degrees?

A. Approximately.

Q. And it would be still producing species X —[but]—slower, right?

A. Yes.

*What a masterful job of cross-examination? Mr. Barney ends up getting "our expert", Dr. Baker, to (**apparently**) agree with his expert, Dr. Crich, that "species X" (i.e. **product #3**) would be formed at 85 degrees. But what if the amount is so small that it cannot be "seen"? For the answer we'd have to wait until tomorrow*—

because the trial then proceeded in confidential session.

Chapter 14
Day Six of the Trial

Wednesday, February 27, 2008

JUDGE BULLOCK: I see the parties have come up with a time schedule for Dr. Baker and D. Hanessian—Let's proceed.

14.1 If Product #3 is Present Theoretically, Is It Really Present?

BY MR. BARNEY:

Q. Good morning, Dr. Baker.

A. Good morning.

Q. When we left off yesterday we were talking about reaction kinetics—I adapted this—[diagram]—from one of the demonstratives you used during your tutorial—-that's sucrose-6-ester with the **adducts on all SEVEN of the available hydroxyl groups**. (emphasis added) correct?

A. Yes—

Q. Okay. And the first chlorine atom when it approaches—**all seven of the —[adducts]—are competing for that chlorination-**(emphasis added) correct?—and—I think you've testified that the 6' position is going to win—most of the time—because it has a lower activation energy compared to the other available groups, correct?

A. That would be an accurate statement.

Q. So we can represent this particular chlorination reaction with a rate constant. Let's just say K1. Would you agree with that?

A. If it's a small k and in italics, those large K's that you have there are equilibrium constants—Minus 5 points on your paper.

Q. It won't be the first time, trust me—The next highest activation energy after the 6' position is the 4 position, correct?

A. Yes—

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Q. All right. And so you have a bunch of chlorine atoms—distributed according to the Boltzmann—[which are]— available to chlorinate at the 6' position compare to the 4 position, correct?

A. —we don't know how many more—we know the ordering.

Q. So they're both occurring simultaneously, albeit at different rates.

A. Yes.

Q. Well, let me see if I can try to improve my grade a little bit. For extra credit I went and got a picture of Mr. Avogadro. Maybe I can earn my points back.

Mr. Barney shows a picture of Avogadro, who was the 19th century Italian scientist who defined the reacting entity in a chemical reaction. This unit is now referred to as a "mole".

A. Yeah, he was a smart fellow, you can tell that by his cranial size.

Q. Now Avogadro is famous for his number. And can you explain to the Court what Avogadro's number is?

A. That's the number of molecules in a mole.

Q. And it's an extremely large number. It's written as 6.022 times 10 to the 23rd (6.022×10^{23}) — and if you were to write all those zeros out, that's what it would look like? (*Referring to the demonstrative).*

A. Exactly

Q. And I actually did this the other day— you have your thousandths place, you have your hundred thousandths, you have got your millions, you have got your billions, you have got your trillions, you have got your quadrillions, and then you can see here that what you have is 602 million quadrillion molecules per mole.

A. Yes.

Q. And the mole is not all that much material. For instance, how many moles of water would you say I have in my cup right here?

A. Well, 18 grams which is a little over three teaspoons full.

Q. So I probably have 20 or 30 moles of water in my cup?

A. I can't see through that cup, but I'll take your word.

Q. So in this cup, I would have—billions of quadrillion molecules swimming around?

A. True.

Q. —every one of those molecules can be moving at a different speed, correct?

A. Yes.

It is now clear where Mr. Barney is going with this elegant piece of cross-examination. He is building up to the proposition, that among these many "quadrillions" of molecules, there MUST be at least some of the 1',6' dichlorinated product #3 (Scheme 7.3). Hence Claim 1 of the 463 patent is satisfied – hopefully?

Q. Okay—you would certainly agree with me that, out of the billions of quadrillions of molecules that are at play in these processes—at least some of them are going [to react] below 85 degrees and form **product #3?**

A. Yes. The Maxwell Boltzmann allows us to make those assumptions, but I would like to illustrate with an example—[there are]—quadrillions of oxygen molecules in this room—[and]—a significant number of them—will collide and give rise to toxic ozone. No one sitting here has worried one bit about ozone—but if over there—I set up an electric discharge—between two poles, in a few minutes—you would smell ozone—[and]—get a headache etc. etc.

But Mr. Barney doesn't give up easily.

Q. You do agree though, there's a few ozone molecules in the room here today, don't you?

A. I do.

Q. And by the same token you'll have to agree that, as a scientific certainty, you're going to have some **product #3** below 85 degrees, correct?

But Dr, Baker is up to the challenge.

A. Yes, but I didn't state how much or—at what levels—relative to the others.

With matter still unresolved, the confrontation moved on to inconsistencies with Dr, Baker's deposition some weeks earlier.

Q. Okay. Now—is it your opinion today that step A of claim 1 requires formation of —adducts **on all seven of the available hydroxyl groups** (emphasis added), did I get that correct.

A. As I interpret the claim, yes.

Q. Let's look at page 100 of your deposition:

QUESTION: Do you think that Claim 1 of then 463 patent requires the formation of an—adduct with every hydroxyl group—?

ANSWER: —I cannot say any more than at least three must be formed—at the three positions that are chlorinated. Whether others form or not, I have no way of knowing.

MR. BARNEY: Your Honor at this point we should probably go on the confidential record.

The confrontation becomes confidential—I am sorry!

The Open Session resumes with a new witness; but Dr. Baker will be back.

JUDGE BULLOCK: Please call your next witness.

MR. SMITH: Good morning Your Honor, JK Sucralose calls Professor Hanessian to the stand.

After the usual formalities, Mr. Smith tenders "Dr. Hanessian as an expert in carbohydrate chemistry".

14.2 An Expert Witness on Both Sides of The Litigation? What Happens Now?

BY MR. BARNEY:

Q. Good morning, Dr. Hanessian?

A. Good morning Mr. Barney.

Q. We met just before Christmas last year?

A. Yes we did.

Q. We spent two wonderful days together?

A. Absolutely.

Q. Discussing sucralose chemistry?

A. Yes.

Wow! It is no wonder that Mr. Barney considers those two days "wonderful", since that was when he crafted his "wedge" relating to the Mufti patent, that he used against Dr. Baker yesterday - and to which he would soon return.

So effusive was Mr. Barney's charm, that His Honor was forced to comment:

JUDGE BULLOCK: Doesn't get any better than that I would imagine.

MR. BARNEY: No, Your Honor. It doesn't, especially with someone as pleasant as Dr. Hanessian.

Oh boy! Our side had better watch out.

With these fulsome pleasantries out of the way, Mr. Barney returned directly to the troublesome Mufti patent.

BY MR. BARNEY:

Q. One of the things that you discuss in your —rebuttal witness statement is the Mufti patent, correct?

A. Yes.

Q. And let's just take a quick look at your rebuttal witness statement—just confirming that you did in fact consider the Mufti patent—

A. All right.

Q. Now, of course, you understand this is an important case for everybody in the room, and you I'm sure you read the Mufti patent very carefully?

He throws down the Mufti/Khan gauntlet

A. I did.

Q. And you're an experienced carbohydrate chemist?

A. I think so.

Q. —[with]—50 years of experience—?

A. More or less.

Q. And—you used that experience to understand what is being disclosed in Mufti, correct?

A. Yes

Q. And it was your conclusion—that Mufti does **not** *(emphasis added)* disclose each and every limitation of the 463 patent, correct?

A. After reading the Mufti patent, because the process is conducted in a different way, I can conclude that not every limitation, or every element in Claim 1 is met in the Mufti patent.

Q. And specifically, it doesn't disclose forming —[salt **B**] *(see Scheme 7.4)*— in the presence of sucrose 6-acetate does it?

This brought an objection by Mr. Smith who said that the questioning was getting into areas of "invalidity" and that Dr. Hanessian was not being presented as an expert to testify "concerning ***infringement issues or claim construction issues"*** *but NOT invalidity issues.*

Until now, I had not realized that a witness cannot be cross-examined about every and any thing that the opposition's lawyer deems fit. Or, at least, so it seemed from Mr. Smith's objection.

MR. BARNEY: Your Honor, **Dr. Hanessian is on our witness list as well** *(emphasis added).* So, to the extent that it cures Mr. Smith's objection, we will call Dr. Hanessian at this time as our witness.

MR. SMITH: I just was looking at their witness list, I didn't see Dr. Hanessian's name on it— Your Honor.

To my surprise, an expert witness can be on BOTH sides of the litigation!

This caused the judge to summon the busy-as-a-bee lawyer Mr. Goulet.

MR. GOULET: Your Honor, I can say it's my understanding — **that we reserve the right to call all Respondent witnesses as adverse witnesses, as they did with respect to Complainants.** *(i.e. as "we" did to "them"?).* Dr. Hanessian has been called. Therefore we did reserve the right to call him as an adverse witness. I don't have a hard copy. I have it on a screen. I invite Counsel to come view it on your computer in the back of the room—

MR. SMITH: I'm looking at an electronic copy, they did say **ANY** witness that Respondents call.

This made me wonder, with some trepidation, whether or not I was also going to be called as an "adverse witness".

With the new information, we had no idea whether Dr. Hanessian was with us (the Respondents) or with them (the Complainants); the next few exchanges did not make us feel more secure.

Q. So, Dr. Hanessian, — Mufti doesn't meet every limitation — [because] — it doesn't disclose forming salt **B** in the presence of sucrose-6-acetate, correct *(See Scheme 7.3)*?

A. In those specific words, he does not form salt **B** in the presence of sucrose-6-acetate

Q. Instead, what it discloses is preforming salt **B** and then adding sucrose-6-acetate to that preformed salt, correct?

A. He forms salt **B** and then adds sucrose-6-acetate to that preformed mixture.

Q. And you agree that that's different than forming salt **B** in the presence of sucrose-6-acetate correct?

A. It is operationally different.

Oh Boy! Looks like we will have to put away our "in situ" Swords of Damocles.

Q. Right. And of course you understand that to anticipate a claim each and every limitation has to be found in a single reference, either expressly or inherently, correct?

A. I understand that.

Q. And therefore, that's why you concluded that the Mufti patent does **not (emphasis added) anticipate the claims** *(emphasis added)* of the 463 patent?

A. That's my understanding.

Q. —Now, I want to show you a portion of Dr. Baker's expert report—Dr. Baker concluded—that Mufti discloses **all of the elements of Claims 1 through 3** *(emphasis added)*—I just want to make clear that you disagree with Dr. Baker on that, correct?

A. **Well, obviously, he has his opinion.** *(emphasis added).*

Mr. Barney had done a masterful job. The series of questions about (a) what was added to the solution and (b) what was already present in the solution was beautifully orchestrated. The only problem is that the operational sentence from the Mufti patent that prompted this line of questioning is the following:

"The reagents (i.e. the salt) may be formed ***in situ*** *but are preferably prepared in advance and isolated before being used."*

The "reagents" in question is salt ***B****, and the sentence says nothing about what other reactants were already in "the solution" itself.*

But with the thin edge of his wedge now firmly inserted between two experts for the Respondents, Mr. Barney would now drive it farther in.

And now I got brought into it:

Q. And if we could look at— the direct statement of Dr. Fraser-Reid — and you know Dr. Fraser-Reid is the expert for GDFII and Niutang?

A. I know Dr. Fraser-Reid, yes.

Q. —Now — the law firm that hired you represents JK Sucralose, correct, sir?

A. Yes it does.

Q. And as we've established here, you didn't put in a witness statement — where you opined about the validity of the 463 patent?

A. I did not.

Q. So I take it that the law firm that had you testify on behalf of JK Sucralose did not ask you to present any opinions about validity in this case?

This was surprising to me, because infringement of the 463 patent was central to the lawsuit, and questions about its validity were germane.

Indeed Judge Bullock was apparently also surprised:

JUDGE BULLOCK: I'm sorry for interrupting. I'm not clear on the answer—are you agreeing with counsel that—the law firm did not ask you to present any opinions about validity?

THE WITNESS: That's my understanding.

JUDGE BULLOCK: You agree with that?

The judge wanted to make sure he had heard right.

THE WITNESS: I agree with that, Your Honor.

Evidently I am not the only one who is confused. Maybe if Dr. Hanessian has been asked to "present any opinions about validity", it would be 'discoverable' and he could have been cross-examined about it?

And this admission gives Mr. Barney more grounds for speculation.

Q. Dr. Hanessian, are you aware that JK Sucralose—has taken a position on the validity of the 463 patent?

A. I'm not aware of that.

Q. And, Dr. Hanessian, what JK Sucralose said in prehearing brief is that JK Sucralose incorporates — the arguments set forth by the other Respondents in this investigation, and they reserve the right to rely on those arguments. Do the attorneys — **I'll withdraw that question. I don't want to know the answer** *(emphasis added).*

Which question is Mr. Barney withdrawing? What question is he not asking, because he does NOT want to know the answer?

Could it be that the question that Mr. Barney has so cleverly NOT asked is something like this:

'Do the attorneys for the different Respondents discuss with one another the arguments that they intend to use?

If they did, would that be so bad?'

Is this the question that Mr. Barney has withdrawn without actually asking it?

Is it possible that rather than ask Dr. Hanessian, its own expert, to submit a relevant argument, JK Sucralose had chosen to rely on arguments set forth by Drs. Baker and Fraser-Reid, experts for other Respondents?

Why would Dr. Hanessian's lawyers, support the position taken by the other Respondents' experts without consulting him? How strange?

14.3 The Words "In Situ" Again: Is the Sword of Damocles in Trouble?

Having now used Dr. Hanessian's testimony to separate him from Drs. Baker and Fraser-Reid, the other Respondents' experts, Mr. Barney could return to these troubling seven words in Mufti's patent:

"The reagent may be formed in situ —."

Cross examination of Professor Hanessian continues:

BY MR. BARNEY:

Q. Now, what I'd like to do now is to take a look at some of those arguments that JK Sucralose is incorporating— Hebei Sukerui prehearing brief — says that "Sukerui Respondents interpret the term 'in situ' to mean that all the reagents — may be mixed together in one vessel and reacted".

A. I see it

Q. And you disagree with that, don't you?

A. Well, it depends on what the term 'in situ' means. I have to admit, having read the Mufti patent, that it's not very clear what he refers to —as in situ. In situ could be **A** added to **B** and **C** or any other combination thereof.

Oh my goodness! This crucial point of "semantics" intrudes again (as it had in Dr. Baker's cross-examination) and this will not make Mr. Barney happy.

Q. But it's your opinion, sir, that Mufti does not disclose forming the –[Vilsmeier salt **B**]– in the presence of the sucrose-6-acetate, correct? I think we have already talked about that this morning?

A. Yes we did, but again, because it's vague in one scenario, if sucrose-6-acetate is one of the components — if I stretch 'in situ', it could — be a possibility.

Nice try, but— this causes Mr. Barney to become very stern

Q. I'm not asking you to stretch. It's your stated opinion — during your deposition that Mufti does not disclose the formation of —[Vilsmeier salt **B**]— in the presence of the sucrose-6-acetate, correct, sir?

A. I don't know if I said that in my deposition. Perhaps I could look at it.

Q. Sure. Let's have your deposition transcript —

QUESTION: "But in terms of the requirement that you add the acid chloride to a preformed mixture — can you show me specifically where that's taught in Mufti?

"ANSWER: As I said, Mufti does it in a different way. He prepares his Vilsmeier reagent in the flask and adds the sucrose acetates to it.

"QUESTION: Are those the same thing or is there a difference?

"ANSWER: It's a difference."

Q. That was your testimony, right?

A. Yes—that is exactly what he [**Mufti**] does *(emphasis added).*

So what Dr. Hanessian had said in his deposition, that had caused concern for "our" lawyers (Mr. Hnath and Mr. Paitnik), had now surfaced again, and Mr. Barney does not let up.

Q. And so — using your experience as a carbohydrate chemist, –[Mufti]— **doesn't** *(emphasis added)* disclose the process that Hebei Sukerui *(one of the Respondents)* explained in their brief —?

A. It does not disclose it in those words, but again, the word 'in situ' is sort of vague to me. I will just leave it at that.

But Mr. Barney is certainly not going to "just leave it at that".

Q. Well, the word 'in situ' means in the pot, correct?

A. It's a Latin word that means in the pot or in the site.

Q. And on that point, you and Dr. Crich are in **complete** agreement *(emphasis added)*?

A. We are, there is no **order of addition in the terminology** of in situ *(emphasis added).*

So is he really acknowledging that he is on the same side as Dr. Crich, the opponents' expert?

But—there is a required ***"order of addition in the terminology"*** *in the contentious seven words of the Mufti patent:* ***The reagent may be formed in situ —*** *although this information was blunted by Mr. Barney's skillful, aggressive cross-examination of "somebody as pleasant as Dr. Hanessian", as Mr. Barney had earlier described the witness. If the reaction involves A + B + C, and Mufti's* ***REAGENT*** *is formed from B + C, then if we mix A + B or A + C nothing will happen, because B + C have not met (see Preamble, Sect. 8.3.3).*

But the last sentence by Dr. Hanessian appeared to substantiate the first claim of the 463 patent which says:

"(a)— adding — an acid chloride to a reaction mixture containing — [sucrose-6-acetate]— to form — salt **B–** ***in the presence*** of said — sucrose-6-acetate—"

And so Mr. Barney had confirmed that Professors Crich and Hanessian were now on "his" side (i.e. the Complainants)!

Does this agreement mean that the "in situ" dispute no longer threatens to invalidate the 463 patent? Only Judge Bullock can say.

14.4 Product #3 Separates the Two Experts

And with this accomplished, the cross-examination moves on to another contentious aspect of the 463 patent (see Scheme 7.3), which states that after heating to 85 degrees, compounds ***products #1****,* ***#2*** *and* ***#3*** *are formed. If the inventors of the patent had merely said 'after heating to 85 degrees, three* ***intermediate*** *compounds were detected', there would have been no problem. But they had given precise and specific structural information about the three intermediate compounds, and it was therefore reasonable to ask about the evidence for the structural assignments.*

Since the 1' position is particularly unreactive, the formation of the 1',6' chlorinated ***product #3*** *was a major bone of contention between "them" and "us". Tate & Lyle could not simply say that they just 'assumed' that* ***product #3*** *had been formed, because that would mean that they had provided uncertain evidence to the patent office.*

This issue would now lead to few degrees of separation between Dr. Hanessian and Mr. Barney. Dr. Hanessian's troubling deposition was again brought in.

Cross examination of Professor Hanessian continues:

BY MR. BARNEY:

Q. Okay. Now, you're aware that step B of Claim 1 of the 463 patent requires the formation of a mixture consisting essentially of **products #1, #2** and **#3** correct?

A. That's the language of step B, yes.

Q. And we've talked quite a bit about that at your deposition. And it's your opinion—that those three species will inherently form below 85 degrees, correct?

A. Well, I'd like to discuss that with you—

Q. —I'm going to point out, when I asked you the question about whether these species would be present in Mufti, you said it's inherent, that was your testimony, correct?

A. Yes, and I'd like to explain myself.

Q. Please do

Confronted with what he had said in his deposition, Dr. Hanessian sought to clarify with a lengthy reply which opens and concludes with the following sentences:

A. All right. So it is my opinion, has been and always is, that there is no factual confirmatory or unambiguous evidence that—[**product #3**]—is formed or is present in these reactions.— In my mindset, that dichloro-6-ester is [**product #2**] and not [**product #3**]. I hope I've clarified my position on that, Mr. Barney".

No way was Mr. Barney going to accept this reversal, for Dr. Hanessian was now saying that there was ONLY ONE dichloro compound, the logically expected ***product #2****, at 85 degrees—not TWO as the 463 patent states. And to make matters worse, in his lengthy clarification, Dr. Hanessian had said: "There is no factual evidence that the species* ***product #3*** *is formed."*

Q. Well, you've clarified it today, but you are going to have to agree with me that that's different from what you said at your deposition. You didn't explain any of that **stuff** *(emphasis added)* at your deposition when you answered my question, did you?

JUDGE BULLOCK: Excuse me. Where does this come from?

MR. BARNEY: Sir, this is his deposition transcript. I think we are on page—

And after attending to the judge's inquiry, Mr. Barney continued somewhat sharply:

BY MR. BARNEY:

Q. Now, Dr. Hanessian, you understood perfectly well that I was talking about a claim limitation. I used that exact word in my question.

A. Yes, to the extent that I understand the law, yes.

But unfamiliarity with "claim limitation" law was not Mr. Barney's concern.

Q. And you understood perfectly well that that claim limitation — requires two different dichloros. And in response to that question—you told me it's inherent.

A. Well, it's a frame of mind — I've maintained — that I did not believe that **product #3** can form. I'm in that mindset — and your cross examining skills may have overwhelmed me at that moment, and I said inherent, and I'm qualifying that based on my conviction that **product #3** is not present at 85 degrees.

Q. Now you do agree that **product #3** will form at some temperature?

A. I don't agree with that either. There is no evidence in the literature or elsewhere that **product #3** is going to form when the 4- position has not been chlorinated already.

This is not going the way Mr. Barney had hoped, because the distance between him and Professor Hanessian is getting wider and wider, so he brings up an additional document—Dr. Hanessian's expert report.

(As an aside, I was struck by the fluidity with which just about all the lawyers could jump from one document to another, retrieving the most minute detail instantly).

Q. Let's take a look at your what you said—in your initial expert report:

" Therefore—one skilled in the art would have understood that in a process to produce —[trichlorinated compound **product #4**]—the reaction would first have produced a— (monochlorinated derivative)—followed **by a mixture of dichloro**—[sucrose-derivatives, followed by the desired trichlorinated —derivative—as recited in the claims." *(emphasis added).*

That was in your expert report, correct, sir?

A. Yes, but I'm not saying 1'-6'-dichloro.

Q. Okay. Well, let's just talk about this for a second. What's the most prevalent dichloro-6-ester you would expect in this process?

A. 4-6' *(i.e. compound **product #2**).*

Q. What's the very next most prevalent dichloro species you would expect?

A. My expectations have nothing to do with reality, Mr. Barney.

OUCH!

Q. Dr. Hanessian, you've had 50 years' experience in this field, and you've told me that it's reasonable to draw conclusions based on your knowledge. Based on your knowledge of this chemistry, what is the very next most likely dichloro you're going to get after **product#2**?

A. At what temperature?

Q. At any temperature?

A. I cannot answer that question if it says any temperature.

OUCH again!

Q. So, when you talked in your initial expert report about a **mixture of dichlorinated sucrose-6-esters**— you said it's clear to anybody of ordinary skill in the art — to understand the most likely dichloros in the mixture are **products #2** and **#3**, correct, sir

Professor Hanessian now goes on to explain that his answer had been based on "prior art", and that he had included the 463 patent as prior art. Clearly a patent cannot be its own prior art, but that issue is lost in what follows. For example, with the following:

Q. How many years of experience in patent law do you have, sir?

A. Nil.

Q. How many years of experience do you have in carbohydrate chemistry?

A. Quite a bit.

Q. When you were discussing all of this **stuff** *(emphasis* added) in your initial expert report, you were discussing the chemistry, correct? You're talking about what a person of ordinary skill in the art would know about chemistry?

A. I was discussing the 463 patent because it's mentioned up there.

Q. Is it your sworn testimony, sir, that you don't expect a mixture of dichlorinated sucrose-6-esters (**products #2** and **#3**) in a process for creating— trichlorosucrose?

A. Again, at 85 degrees, I don't expect it — My position is very clear on what chemistry we'd do if I were to run this reaction myself. I would not see any **product #3.**

But Mr. Barney is nothing if not tenacious. He goes back to Hanessian's deposition and reads a quote which says in effect that ***product #3*** *is "less likely to be formed at 85 degrees —."*

Q. So what you said there was that it's less likely to form?

A. Right.

Q. Leaves open the possibility that it may form?

A. Yes. If that's how you understand it. I obviously misspoke, and I was in error in interpreting that.

Q. So now it's your testimony — that the possibility of it being formed is zero, it can't be formed?

A. That is my testimony.

At this stage, Mr. Barney seems resigned to Dr. Hanessian's obstinacy, but nevertheless quotes again from the troubling deposition probably to convince the Judge that the witness had undergone a change of mind:

Reading from Hanessian's deposition:

"QUESTION: But at some point below 85 degree, you would have a mixture of—[dichloros]—, even though the 1'-6' might be just a small portion of that.

"ANSWER: I would expect the monochloro and **one of the dichloros to be products at 85 degrees** *(emphasis added).*

"QUESTION: but in terms of what you call a mixture of the dichloros—just a small—smaller quantity of the 1'-6', right?"

BY MR. BARNEY:

Q. This is actually kind of interesting. Mr. Smith *(Hanessian's lawyer)* objected, and then YOU objected. And I explained to you that only he gets to object. We did have a good time at your deposition, didn't we?

A. Absolutely.

But the "good time" was running out, because the Respondent's experts Hanessian and Baker, had been reunited, with concomitant cleavage of the momentary bond to Complainant's expert Crich, which had been formed over the meaning of 'in situ'.

The morning session ends with Judge Bullock suggesting a lunch break, which earned the following:

MR. BARNEY: The only reason I would proffer, Your Honor, is that I'm tired—and I certainly would concede to your wishes.

If Mr. Barney was so tired, he has Dr. Hanessian to blame.

14.5 The Kentucky Derby, Maxwell–Boltzmann and Product #3

After lunch, Dr. David Baker returned to the stand to be further cross-examined by Mr. Paulraj, from the International Trade Commission Staff.

He begins by returning to the thorny issue about the likelihood of ***product #3*** *being formed at 85 degrees. Since there is absolutely no direct evidence for the formation of this compound at 85 degrees, Tate & Lyle has been relying heavily on the Maxwell-Boltzmann collision theory about distribution of energy in molecules that are reacting. The theory, supposedly, allows the possibility, that there will be enough energy to give just a A TEENY AMOUNT of* ***product #3***

In Sect. 9.1 I offered one simplifying concept of Maxwell Boltzmann distribution theory. Below I offer another:

Three chlorines are to be installed in going from sucrose-6-acetate to ***product #4*** *(Scheme 7.3), each of which requires a different amount of effort. The chloride at the 1'-position is the most difficult, and so requires the greatest amount of effort. However, according to the Maxwell-Boltzmann theory, even at 85 degrees, it is possible to induce* ***some amount*** *of reaction at the most difficult site. So some reaction at position 1' is happening albeit slowly, and to a very, very, very, very, very— small extent.*

How small? One may reasonably ask. Tate & Lyle would probably argue that it does not matter how small. The theory does NOT predict quantity. ***But what if it is so small that the laboratory instruments, that chemists normally use to identify compounds, cannot to detect it? If it is not 'visible' to my instruments, does it exist?***

In other words "If a tree falls in the forest, when there is nobody around, does it make a noise?"

This raises philosophical questions about theory and empirical results, as well as the nature of "proof".

Is this litigation now at the mercy of these age-old polemics?

BY MR. PAURAJ:

Q. Good afternoon, Dr. Baker.

A. Good afternoon.

Q. I want to follow up with some questions that Mr. Barney had asked you.

(Mr. Paulraj holds two degrees from Case Western Reserve Engineering School in biomedical engineering and in polymer science, and he draws heavily upon this background in his questioning).

The first 20 pages of the transcript are an intricate examination of several diagrams that were put into evidence by other witnesses. It was interesting—IF you had the diagrams in front of you. But they are NOT part of the public transcript, so I cannot comment on them.

But something else, which was more interesting, soon came up.

Dr. Baker, who teaches at the University of Tennessee, had offered another simplification of the Maxwell-Boltzmann theory that is redolent of his proximity to the state of Kentucky – home of the Kentucky Derby. Mr. Paulraj draws upon this.

Q. —Doctor—earlier today—you made an analogy to racehorses, do you recall that?

A. Yes. I was trying to take—this complicated Maxwell Boltzmann—out of statistical mechanics and collision theory into something that's understandable—

Remember now, that the starting compound sucrose-6-acetate, has seven free-OH groups. Dr. Baker will be comparing these to seven racehorses. All seven of the –OH groups can ***potentially*** *be replaced by chlorine (i.e. each racehorse can POTENTIALLY win the Derby); but we are only interested in 1st, 2nd, and 3rd places, the expected order being 6', then 4, then 1'.*

Q. —you said there were seven different racehorses, and they each have different [speeds]—, is that right?

A. Yes.

Q. And so they are trying to get to the [6',4 and 1' positions] of sucrose-6-acetate.

A. Yeah, get past the flag.

Q. So—the horse [that is] racing to the 6'position—would be the fastest horse, is that right?

A. Yes, —that's a Kentucky racehorse.

Q. I'm not a big race horsing fan, but I'll try to follow it up after this, Dr. Baker. So the next fastest horse would be the 4-position, isn't that right.

A. Yes, that's the County champion.

Q. And the 1'position racehorse, that would be the third fastest?

A. Yeah, that's the one down in the county race.

Q. You still get some money if you bet on the 1' though, wouldn't you?

A. Well— if you bring a Kentucky racehorse into a county fair, that racehorse is out-of-there, gone, and the rest of them are trying to figure out where to go—.

Q. Doctor—would there be any situation where the horse that corresponds to the 1'position–[could be]—faster than the horse that corresponds to the 4 or the 6'position?

A. I couldn't imagine it—

Q. So when you raise the temperature —in our hypothetical analogy at the racetrack, would all the horses go a little faster?

A. Yes.

Q. And this analogy is consistent with the Maxwell-Boltzmann distribution?

A. It is.

This interchange between Mr. Paulraj and Dr. Baker has been brilliant - and entertaining. The carefully crafted questions, succeeded in reducing some sophisticated chemistry to layman terms, without (too much) damage to the core principles.

But Mr. Paulraj had not finished. He returned to the issue of direct versus indirect evidence concerning the transformation of sucrose-6-acetate, to the trichlorinated ***product #4*** *(Scheme 7.3).*

Professor Baker had obtained a sample from Hebei Sukerui the Chinese manufacturers for which he was an expert witness. The transformation of sucrose-6-acetate to ***product #4*** *had been interrupted at 85 degrees to obtain the sample, and he had subjected it to mass spectrometry. This instrument would enable him to get a good idea of what compounds were present in the sample.*

BY MR. PAULRAJ:

Q. —you recall Mr. Barney had asked you about the difference between direct and indirect evidence?

A. Yes.

Q. And do you believe that this mass spec. study — is direct evidence that compound— **product #3**— is not formed in the sample of Hebei Sukerui that you had tested?

A. Well, could I hear that one again?

MR. PAULRAJ: If I could have the court reporter repeat it.

THE WITNESS: Yes, please.

MS. SUNDEEN: Your honor, this information is confidential.

MR. PAULRAJ: I apologize—This actually should go confidential.

But before Judge Bullock could rule on the matter, there were some fireworks.

MR. BARNEY: Your Honor, we object to this exhibit. This was part of the test data that was struck — and I don't think I raised this—in my cross [examination].

And he was immediately joined by his senior colleague.

MR. JARVIS: Certainly, Your Honor, Staff has objected to Tate & Lyle's use of this information. Staff shouldn't be allowed to use it.

MR. PAULRAJ: I apologize, Your Honor, I thought this was in because it was in the rebuttal witness statements that were handed out yesterday.

Whereupon the Court went into confidential session.

I am not at liberty to disclose what was said during the confidential hearing; however, from what followed when the open session resumed, I do not think that Tate & Lyle's attorneys were happy with the ruling, for it induced trenchant comment from Mr. Jarvis, the senior counsel:

MR. JARVIS: Your Honor, it's our ability to cross-examine all their witnesses that's now being invaded, as more of his *(Mr. Paulraj)* time accumulates. Basically, Mr. Paulraj is using leading cross questions to rehabilitate their witness. The anomaly here, and we understand that you give the Staff certain liberty.

JUDGE BULLOCK: — “Right.”

MR. JARVIS: But the anomaly is that Mr. Paulraj is rehabilitating Respondents’ witnesses with leading cross testimony much to our disadvantage, and, now, going over time that we’d otherwise be entitled to cross-examine their witnesses. Our opportunity for cross-examining their witnesses is being invaded. That’s the fundamental concern.

The “fundamental concern” arises because there are time constraints owing to the fact that the judge has made it clear that the trial has to be finished in 2 days time.

MR. PAULRAJ: I have very few questions — this is actually the last document that I am going to ask Dr. Baker about.”

And with this, Mr. Paulraj’s cross-examination continued.

BY MR. PAULRAJ:

Q. I’ll try to speed things along, Doctor. So based on the requirement of this document, do you believe that the information that the inventors had — (for)— the 463 patent, would be sufficient to publish in a journal such as the Journal of Organic Chemistry, in which they reported formation of **product #3** at a temperature below 85 degrees Celsius?

A. I have seen no data that would identify that authentic sample — meeting those criteria of identify and purity.

And Mr. Paulraj finally concludes with this:

Q. —with respect to your obviousness opinion, would you also agree that if there is no evidence that **product #3** has formed — the prior art does not render the 463 patent obvious?

A. If you are requiring the identification of **product #3** as an element of that claim — then it’s not identified in any of the prior art, correct.

MR. PAULRAJ: Thank you Doctor. Thank you Your Honor.

*To my mind, the last two pairs of question/answer comments take the 463 patent in different directions. The first answer, by denying the presence of **product #3,** meant that the patent had committed a falsehood, and therefore should be invalidated. On the other hand, the second answer, by denying obviousness, seems to validate the patent, because the chemistry on which the claim was based was not obvious from prior art or literature.*

So should both sides be satisfied with the split that ended Mr. Paulraj’s cross examination? Not very likely!

MS. SUNDEEN: Your Honor, Could you confirm for me that, if I don’t have any redirect for Dr. Baker, he is then free to go?

JUDGE BULLOCK: Yes, that’s correct. If you have no redirect—there’s no need for recross.

Really? That’s what Judge Bullock hoped.

MR. BARNEY: Your Honor, we would like the opportunity to recross because what Mr. Paulraj did was certainly cross-examination. It was nothing but leading questions.

JUDGE BULLOCK: I apologize. I wasn’t focused on that concern. Obviously, if you have—no redirect, there are going to be no questions from them *(i.e. Ms. Sundeen)* regarding your redirect. However, I think it is fair— since I generally give such wide latitude to Staff, to allow Complainants to follow up on Staff's questions. So in light of that, what is your preference?"

MR. BARNEY: Just a few things Your Honor.

Recross examination by Mr. Barney.

Q. Dr. Baker, I'd like to continue the discussion about your testing, your mass testing, and I think there is something we need to clear up.

Clearly, if Mr. Barney is going to "clear up" Dr. Baker's mass spec study, he will have to find out more about the sample that was used for his analysis. This sample was obtained from Hebei Sukerui, one of the alleged patent infringers. Is it fair to use this sample to draw any conclusion about the presence or absence of ***product #3*** *in the Tate & Lyle patent? Hebei Sukerui claims that their manufacturing process is different from Tate & Lyle's. But how different? Mr. Barney would obviously want to know all of these issues, therefore, not surprisingly, Mr. Sundeen is quickly on her feet.*

MS SUNDEEN: "Your Honor, This is confidential — it's Sukerui confidential
JUDGE BULLOCK: Let's go on the confidential record.

And regrettably, I am not at liberty to disclose what took place during the confidential session.

Chapter 15
Days Seven and Eight of the Trial – My Time on the Witness Stand

My appearance before Judge Bullock began after lunch on the seventh day, Thursday, February 28, 2008, and continued on Friday morning 29th, the eighth and final day of the trial.

JUDGE BULLOCK: Please proceed.

MR. HNATH: Thank you, Your Honor. And the GDFII Guangdong Respondents would call Dr. Bertram Fraser-Reid as our next witness.

Whereupon—

DR. BERTRAM FRASER-REID

A witness, called for examination, having been duly sworn, was examined and testified as follows:

15.1 Re-Direct Examination by Mr. Hnath

Q. Good Afternoon, Dr. Fraser-Reid.

A. Good Afternoon, Mr. Hnath.

Q. Could you turn to your witness binder and locate RX-561 C, please? And is this your direct witness statement?

A. Yes.

Q. And, Dr. Fraser-Reid, does this contain your own answers in response to questions from counsel?

A. Yes, it does.

Q. And could you please —make sure that we have an original signature—and put today's date, February 28th, 2008?

A. Done.

Q. Dr. Fraser-Reid, could you turn to RX-828 C, please? And is this your rebuttal witness statement?

A. Yes it is.

Q. And does this statement also contain your own answers in response to questions from counsel?

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_15,

A. Yes, it does.

Q. And could you please—sign and date the document? I think the date is February 28th.

A. Thank you.

MR. HNATH: Sometimes, Your Honor, it's easy to lose track of the days when you're in a hearing like this.

JUDGE BULLOCK: Absolutely.

MR. HNATH: And, Your Honor, we would offer Dr. Fraser-Reid as an expert in carbohydrate chemistry and comparative organic synthesis.

JUDGE BULLOCK: Okay.

MR. HNATH: And with that, Your Honor, we would offer Dr. Fraser-Reid for cross-examination.

JUDGE BULLOCK: Thank you.

MR. PAULRAJ: Your Honor, Staff has agreed to go first in its questioning.

JUDGE BULLOCK: I believe that was the agreement with the Complainants.

15.2 Cross-Examination by Counsel for the International Trade Commission Staff

My first tormentor was to be Mr. Paulraj from the Office of Unfair Import Investigations (see Chap. 8). Anxiety consumed me. As noted above Mr. Paulraj holds two graduate degrees in Engineering, and he had shown his mettle as a lawyer by his searching cross-examinations of Drs. Crich and Baker. Even of more concern, he had earned the displeasure of Tate & Lyle's lead attorney, Mr. Jarvis, who was not happy with the questioning of my fellow expert, Professor David Baker, and said so clearly : "Mr. Paulraj is rehabilitating Respondent's witnesses with leading cross testimony much to our disadvantage —"

Would Mr. Paulraj now be forced to tilt towards Tate & Lyle attorneys so as to restore "fair and balanced" lawyering?

My angst was not lessened when he went directly to my Vilsmeier salt polemic.

BY MR. PAULRAJ:

Q. Good afternoon, Dr. Fraser-Reid.

A. Good afternoon, Mr. Paulraj.

Q. Now you refer to the term "Vilsmeier salt" in your witness statement?

A. Yes.

Q. And do you understand—[it]—to be the same as the chloroformiminium chloride salt [*i.e. structure **B**, Scheme 7.4*] that's required by claim 1 of the 463 patent?

A. Yes, if you Google "Vilsmeier salt," that's what comes up.

Q. Let's turn to your answer to question 16 of your direct witness statement.

A. 16, Yes.

Q. —you state that "I use the term 'Vilsmeier salt' to refer to chloroformiminium salt [*i.e. structure **B**, Scheme 7.4*]. I note, however, that the term "Vilsmeier' itself can generally refer to an addition of an acid to a tertiary amide, such as DMF [*i.e. structure **A***, *Scheme 7.4*], and is not limited to the salt form." Do you see that?

A. Yes.

Q. Let's go to the 463 patent, column 4 line 8—[it]—defines what chloroformiminium chloride salt is, doesn't it?

A. Yes, in line 10 and 11.

Q: So it is your understanding that a chloroformiminium chloride salt is really one type of Vilsmeier salt?"

A. Yes, it has evolved into that over the years.

Mr. Paulraj's cross-examination helped me to elaborate on details of the Vilsmeier reaction that I had included in my Second Expert Report, and also allowed me to tell the Court that the term 'Vilsmeier' could be used as an adjective as well as a noun. When this issue first emerged during preparation for my Second Expert report, Mr. Hnath (my lead counsel) had restricted the label "Vilsmeier" to the usage in the 463 patent.

But I took advantage of the opening provided by Mr. Paulraj to deliver a tutorial about the history of the reaction in question. I noted that when I was a graduate student, we learned of the Vilsmeier-Haack reagent, as a way to formylate an aromatic ring.

To my great surprise, Mr. Paulraj was so well prepared that he produced a patent to illustrate the reaction I had just described.

Again, I was struck by the amount and extent of the 'digging' that all of these trial lawyers carried out in preparation for the trial, and the dexterity with which they could retrieve these disparate pieces of information at such short notice.

*My questioning by Mr. Paulraj now gets to reaction of alcohols with acid chlorides such as thionyl chloride. Why was the issue important? Remember that to prepare sucralose, we must replace three OH groups with chlorine, i.e.: Sugar-OH→Sugar-Cl. Could this reaction be done directly using thionyl chloride? Probably! But it would be very slow. So as far the 463 patent was concerned, the reaction has to go via the Vilsmeier route so as to be finished in a matter of hours. Hence it is necessary to determine whether the reagent is structure **A** or structure **B** (Scheme 7.4).*

BY MR. PAULRAJ:

Q. In your opinion, Doctor, does Claim 1 of the 463 patent—require that the acid chloride—react with the tertiary amide to form the Vilsmeier type salt—

A. Yes.

Q. And—what's the basis for your understanding that there's a reaction between the acid chloride and the tertiary amide —?

A. Well the oxygen of the tertiary amide carries a substantial negative charge [*as indicated in Scheme 7.4*]—and this allows —[that oxygen]— to react with the acid chloride [*thionyl chloride, Scheme 7.4*]—first—en route to the Vilsmeier salt—.

Q. —Now—in your witness statement—you've drawn—[an]—equation where—DMF may react with thionyl chloride.

A. Yes.

Q. And—you've provided an example of an alcohol reacting with—thionyl chloride?

A. Yes.

Q. And it's very slow, and—you've stated that it requires a catalyst, do you see that?

A. Yes.

Q. And is this—the reason why you need to first form an intermediate such as [salt **B**]?

A. Yes.

Q. If you used **any** type of catalyst, would you be able to directly react the acid chloride with the alcohol?

A. Yes, one needs a catalyst to allow the reaction to proceed in real time. There are cases, of course, where, if you leave it long enough, then you may get away without a catalyst—

Q. Doctor, would pyridine have helped catalyze the reaction between the thionyl chloride and the alcohol—?

A. Yes, pyridine would have been used as a catalyst. *(But pyridine was not mentioned in the patent.)*

15.3 The Mufti/Khan Patent – A Dangling Sword of Damocles

BY MR. PAULRAJ:

Q. You talk about the Mufti reference in your direct witness statement, and you state that the Mufti reference anticipates the 463 patent, is that correct?

A. Yes.

Q. Do you acknowledge that, in Mufti, the preferred way—of chlorinating the sucrose-6-acetate molecule is to [prepare salt **B** ahead of time, *Scheme 7.4*]—before adding it to the mixture of sucrose-6-acetate?

A. Yes.

Q. Why do you think that was a preferred way for Mufti?

A. Well, I think that may be because—that's how Hanessian used it—

Q. So in their preferred mode—they made—[salt **B**]—let it dry overnight and then used it, didn't they?

A. Yes—.

Q. —but why do you think they waited overnight—before doing their chlorination reaction—?

A. Why did they wait overnight?

Q. Yes.

A. They probably had to go home and sleep.

Q. That could be a good reason, Doctor. Is there any scientific reason why they would have —[waited]—before—mixing it with the sucrose-6-acetate?

A. No I can't think of any – but they may have wanted to wait until the morning to start the reaction because —[they don't]—know how long it's going to take—[and]—you don't start a reaction at 5:00 in the afternoon, unless you are a graduate student.

During the cross-examination, I was totally unsure about whether I was answering Mr. Pulraj's questions to the best advantage of "our" side, but I was taking every opportunity to tell the court of my own private convictions. There would now be another such opportunity concerning the ***number*** *of OH-groups that form adducts with the Vilsmeier Reagent.*

BY MR. PAULRAJ:

Q. —in the 463 patent, Doctor, is it your understanding that the O-alkylforminiminium adducts (*see Scheme 7.4)* are always present on the sucrose-6-acetate molecule?

A. Once the Vilsmeier reagent has been formed, you mean?

Q. Always?

A. Yes.

Q. So as soon as you introduce the sucrose-6-acetate into the reaction mixture you're going to have—[adducts]—on all the hydroxyl groups?

A. Well—it's an exothermic reaction *(i.e. produces a lot of heat)* so you need to do it very slowly.

Q. But it'll take some time.

A. Yes, but it is my position that **all seven** hydroxyl groups will become derivatized.

Mr. Paulraj's questioning shifted quickly to issues dealing with tin chemistry, and with the other two allegedly infringed patents – but not before I had made my point about ***"all seven"*** *hydroxyl groups.*

Why was this important?

The thorny issue here, to my mind, was that sucrose-6-acetate has seven-OH groups, but ONLY three would be replaced by chlorine.

Do only these THREE react with the Vilsmeier reagent to give the KEY COMPLEX (Scheme 7.4)?

Why not all seven since they are capable of reacting?

The patent itself was, as the lawyers might say, silent on how many of the seven OH groups did actually react in the KEY COMPLEX, and so that left the matter open to speculation by the experts. I had maintained from the start that all seven would be COMPLEXED, even though only THREE would be REPLACED; however, that view was not shared even by my fellow experts, who had chosen numbers varying from two to five.

Mr. Paulraj's cross-examination had exposed three aspects in which Scheme 7.4 threatened the validity of the 463 patent:

1. *Are all SEVEN-OH groups of sucrose-6-acetate derivatized in the KEY COMPLEX?*
2. *Does sucrose-6-acetate react with intermediate* ***A****, rather than* ***B****?*
3. *Why doesn't thionyl chloride ($SOCl_2$) chlorinate Sugar-OH directly?*

Discrediting the implications expressed in Scheme 7.4, would certainly not sit well with the Complainants, and I fully expected that the issue would resurface again and again during my time in the witness box.

15.4 Cross-Examination by the Counsel for the Complainants

I would next face Mr. Fues for Complainants Tate & Lyle. He had spent two days taking my deposition a few weeks earlier, and so I thought I knew what to expect; but on this occasion his first questions left me speechless.

BY MR. FUES:

Q. Good afternoon, Dr. Fraser-Reid.

A. Good afternoon, Mr. Fues.

Q. I have a background question. In your expert reports, did you follow the same scientific approach that you follow in your research?

I was totally unprepared for this "background question", and muttered appropriately:

A. I'm sorry?

Q. Did you follow the same scientific approach in developing your expert reports in this case that you follow when you are doing academic research?

A. I don't see the connection between them. I work in the lab with chemicals, and I do experiments — I don't do any experiments here.

Q. That's exactly right. You haven't run any experiments here, have you?

A. No.

Q. Do you have any reason to think that the opinions that are expressed in your Witness Statements are erroneous as you sit here?

This left me confused. Did Mr. Fues expect me to conduct experiments in Judge Bullock's courthouse?

A. No.

Q —you provided a construction — (which) — says that it is presumed that all seven hydroxyl groups of sucrose-6-acetate will react with the Vilsmeier salt. Do you recall that claim construction you provided?

A. Yes.

Q. So you are saying that it is **presumed** (emphasis added) — (but not) required. Is that right?—You do not require all seven hydroxyl groups to react with the chloroformiminium salt. Do you?

A. I do. — I say so quite plainly.

Mr. Fues now jumps from my witness statement (where I was examined by my friendly lawyer, Mr. Hnath) to my Deposition where he had been my questioner.

BY MR. FUES:

Q. Could we please have page 118 from Dr. Fraser-Reid's **deposition** transcript. January 7th, lines 3 to 18, please?

My deposition is shown on the screen at the required question and answer.

"QUESTION: Well—is there anywhere in the patent that says **all seven** hydroxyl groups have to react with the Vilsmeier salt?

"ANSWER: No, it doesn't say the seven positions."

BY MR. FUES:

Q. Were you asked that question and did you give that answer, Dr. Fraser-Reid?

A. —yes I did. The word "seven" is not there, but the claim says—could you put up the patent (*on the screen),* please?

I knew that the word "seven" was in the patent, and so would have like it to be shown on the screen; but no luck.

Q. Dr, Fraser-Reid, just a yes or no answer, is that your testimony?

A. No, I cannot give you a yes or no answer, I think it is more complicated than that, the word "seven"—

JUDGE BULLOCK: He said it's more complicated?

THE WITNESS: Yes

JUDGE BULLOCK: Excuse me sir (*to Mr. Fues*). Do you want more than that?

MR. FUES: No, I just wanted to confirm your testimony.

JUDGE BULLOCK: Dr. Fraser-Reid, your counsel on redirect will be able to elicit more testimony.

THE WITNESS: Okay.

JUDGE BULLOCK: So you can clarify your answer.

THE WITNESS: All right.

WOW! Judge Bullock had saved me! Interestingly, according to the court transcript, I never did give a yes or no answer to Mr. Fues. But also the judge suggested that my counsel, Mr. Hnath, could submit me to redirect examination. I would take full advantage of this opportunity next day, as my time on witness stand continued.

The possibility of derailing the 463 patent by means of Scheme 7.4 could not go unchallenged. The slow reaction of thionyl chloride with the alcohol (Sugar-OH) to give the desired Sugar-Cl was one point of attack, and although Mr. Paulraj had already grilled me on this issue, Mr. Fues now takes his turn.

BY MR. FUES:

Q. —Now you have depicted a reaction —and you say that the reaction with alcohol is very slow, and it requires a catalyst. Is that your opinion, that that requires a catalyst for that reaction to take place?

A. For most reactions—thionyl chloride reaction with an alcohol will require a catalyst, yeah.

Q. Are you aware of instances where thionyl chloride will react with an alcohol and **not** require a catalyst?

A. Yes.

I had answered before I realized the trap that Mr. Fues had set for me.

Q. Such as?

I tried to recover.

A. But in this case—I was drawing the comparison between thionyl choride reacting with DMF in the presence of the alcohol—one reaction is going to go faster than the other.

No luck!

Q. I am concerned with the word right here where you say—[it]—requires a catalyst.

A. Okay.

Q. Is it your expert opinion that thionyl chloride requires a catalyst to react with an alcohol?

A. I said before that it requires something like pyridine—that's the standard way of doing that reaction.

Q. Is it your testimony, sir, that thionyl chloride will **not** react with an alcohol without a catalyst?

Q. No, no it will react with it—[but]—it may take some time.

Q. How much time?

A. That's why I said very slow.

Q. How much time, sir would it take?

A. Well it depends on the alcohol—

Q. I'm going to give you a hypothetical. Consider a reaction with octanol as the alcohol, thionyl chloride, and a solvent and no catalyst?

Well maybe two can play this game.

A. What is the solvent?

Q. Ether. Are you going to have a reaction with those components?

A. Yeah, I think so.

Q. And how long will it take?

A. I have no idea.

Q. Do you have an expert opinion on how long that will take?

A. Well, if I wanted it to go quickly, I would use a catalyst.

Q. Well, I'm asking without a catalyst.

A. Without a catalyst. And what temperature are we reacting at?

We play some more!

Q. Say, around zero degrees centigrade.

A. I would expect that to be pretty slow.

Q. How slow sir?

A. Hours.

Mr. Fues would not give up – I can't beat him at his game.

Q. Can you give us a ballpark, how many hours?

And so finally in desperation, I tried another tack.

A. No. As I've told you—in my deposition, chemistry is an experimental science.

Q. So just so I'm clear on your testimony, that reaction would occur, would not require a catalyst, and you can't tell me how long the reaction would take, is that right?

A. I'd have to measure it.

But this only brought my opinion into further disrepute.

Q. Do you think that –[it]—is inaccurate then to say that a catalyst is required for this reaction?

A. It is required in comparison to [the alternative], and I repeat that both equations were being addressed as a pair of reactions.

So Mr. Fues had succeeded in (sort of) getting me into a corner by some fine lawyering. My friend Bill Roush, who had recommended me as an expert witness, had warned me that the lawyers would jerk-me-around. This would now continue by showing that sections of my various documents were not in agreement.

My interpretation of the exchanges which are to follow, does not have the benefit of lawyerly insight of any of the counselors, with me or against me, involved in the litigation. This is therefore a chemist's insight, pure and (possibly) simply.

"We" have made a big issue of the Mufti/Khan patent, saying that it had reported the "in situ" preparation of the Vilsmeier reagent several years earlier. Therefore the report in the 463 patent was "anticipated", and so the patent should not have been issued. This is indisputable – as far as this chemist is concerned.

But "we" became more expansive, and expressed "the opinion that ***Mufti teaches EACH of the asserted claims*** *of the 463 patent".*

Well, one of "the asserted claims of the 463 patent" is that ***product #3*** *is formed below 85 degrees, and so to be consistent, "we" have to say that the Mufti patent somehow "contains"* ***product #3****. We can't have it both ways.*

The problem is that from the standpoint of ***chemistry,*** *there is no way that* ***product #3*** *could have been formed in the Mufti/Khan work. They used a different "starting material", and so could NEVER have obtained* ***product #3.*** *(Okay, they could have got an analog of it).*

So we chemists had to face this illogic in "our" thinking, and Mr. Barney had already made Dr. Baker pay. Now Mr. Fues would have a crack at me.

15.4.1 Mufti/Khan Again – Sword of Damocles Dangles Some More

BY MR FUES:

Q. I'd like to pull up your **initial expert report**—[which states]—on page eight—[that]— "Mufti teaches each of the asserted claims of the 463 patent." Did I read that correctly?

A. Yes.

Q. So at the time you submitted this **report**, you considered the Mufti patent, all by itself, to anticipate each of the asserted claims of the 463 patent, isn't that right?

A. Yes.

Q. I'd like to look at your—**-deposition**—I took in January?

A. Uh-huh.

Q. At that time were you also of the opinion that Mufti teaches each of the asserted claims of the 463 patent and, thereby, invalidates the 463 patent?

A. Yes.

And now he jumps back to my ***witness statement –*** *although he apologizes!*

Q. I apologize for jumping around, but I would like to go back to—[your **witness statement**]—which says that "whether Mufti contains all of the elements of the 463 patent or not **depends in part on how the Court interprets the claims**" (emphasis added). Do you see that?

A. Yes.

Q. You didn't have that qualifier in your—December 3rd **expert report**, did you?

A. No, but—

Q. And you didn't have that qualifier?

MR. HNATH: Your Honor, he interrupted.

JUDGE BULLOCK: If he wanted a yes or no answer, then you can follow up.

MR. HNATH: Okay. Thank you.

My counsel obviously thought I had been interrupted – and I had – but that did not phase Mr. Fues.

BY MR. FUES:

Q. And you didn't have that qualifier when you said that Mufti anticipates the 463 patent during your **deposition** in January either, did you?

Thus the simple phrase ***"depends on how the Court interprets the claims"*** *took center stage. I could not even remember when or why I had made that off-the-cuff remark. But I had to try something—*

A. My understanding of this– was changing—due to changes in the expert witness of Dr. Crich (*for the Complainants)*—[which I]—had to take into consideration.

Q. So you admit you changed your opinion—?

I just can't win!

A. I will say that my opinion evolved following changes that were taking place elsewhere.

Q. —This is, again, in —[your]—**direct report**.—I'll read it into the record. "When I read the 463 patent, I thought the inventors had specifically tested for and found —[**product #3**]?

A. Yes.

Q. At or below 85 degrees?

A. Yes. *But rather than giving Mr. Fues the simple "yes or no" answer that he wanted, I continued reading the explanation that I had written in my direct report:* "I then learned that Navia (*a co-inventor of the 463 patent)* testified that they did not in fact test for—[**product #3**]— separately—but simply made assumptions about what would be in the mix below 85 degrees. Based on my own knowledge, as well as the materials in this case, I don't believe one can assume that the– [two dichloro esters]— are present—"

Mr. Fues was not amused.

BY MR. FUES:

Q. **Dr. Fraser-Reid, you don't need to read your [direct] report into the record.** I have your report. I know what you said. I want to know when you **supposedly** learned, sir, about this **supposed** *(emphases added)* testimony by Dr. Navia, when was that?

A. That was presented to me—I think it was—after my **second expert report** —

Q. So that was **after** submitting your expert reports, is that right?

A. Yes.

Q. —I would like to look, please, at your **initial expert report**—[which]—you submitted on December 3rd, you said you had reviewed the Juan Navia depositions—didn't you?

A. Yes—

Was I lying? Or did I really forget when the document was given to me? I could take the Fifth. (The "fifth" amendment of the United States Constitution says, approximately, that you don't have to admit that you lied, if you lied).

(Recall from, Sect. 9.2, that Dr. Navia would be considered an "adverse witness" if "our side" called him to the stand).

Q. Now when we were at your deposition in January, you indicated that—your lawyer had supplied you with the assertion about these assumptions that were allegedly made about [**product #3**]— do you recall that?

A. Well, he made me aware of the deposition the he had taken with Navia.

JUDGE BULLOCK: Let's take a break.

Whew! No a moment too soon for me. I was no longer sure of what I had said when I said it – but I didn't get much time to pull myself together, because the break was soon over.

JUDGE BULLOCK: Please proceed.

BY MR. FUES:

Q. Dr. Fraser-Reid, before we left, I had brought up the point—that shortly before [your] **deposition** [on January 7th], your lawyer had supplied you with the assertion that Juan Navia had made assumptions about whether **product #3** existed in the chlorination mixture, do you remember that?

A. Yes.

Q. If you disregard how your lawyer characterized the Navia **deposition** testimony, you would still believe that—[**products #2** and **#3**]—are formed below 85 degrees?

A. No, not [**prod**—]

I was interrupted.

Q. And if you disregard what your lawyer said, would you have believed that these intermediates *(i.e.* ***products #2 AND 3****)* are also formed in Mufti?

A. At a particular temperature or just formed, period?

Q. Below 85 degrees.

A. No.

This is getting intense. The battle between Mr. Fues and me illustrates one difference between law and chemistry. In the lab, or in the factory, <u>it would really NOT matter whether</u> ***<u>products #2 and #3</u>*** *<u>were formed, as long as we ended up with</u>* ***<u>product #4,</u>*** *the desired precursor of sucralose (Scheme 7.3). But if "we" can* *convince Judge Bullock that* ***product #3*** *is not formed, the patent could be seen as being inaccurate. So the game had to go on.*

Mr. Fues will not let up.

Q. Can we please have Dr. Fraser-Reid's **deposition** testimony at page 159—lines 3 to 18?

"QUESTION: —could we take a look at the date of your **expert report,** which was on December 3rd of 2007, just a little bit over a month ago—Before your lawyer gave you his argument.

"ANSWER: Yes.

"QUESTION: Based on your 47 prior years of experience, did you think that **product#3** was formed below 85 degrees?

"ANSWER: Well I would have said yes, because if it's formed in the 463, there's no reason it shouldn't form in Mufti, with that as precedent."

I think I goofed with this answer. To say that "there's ***no reason*** *it shouldn't form" is not proof that it actually did form! But this illogic was not Mr. Fues' problem, it was mine. Indeed it played into his hands. So he continued:*

Q. Dr. Fraser-Reid, you never went back and verified Juan Navia's deposition—regarding **product #3**—did you?

A. Yes, I did.

Q. And you recall him [*i.e. Navia]* saying exactly what your lawyer has told you he said?

A. Well, my lawyer gave me the document, and I read it, and it said that they had not actually characterized **product #3**, Your Honor. They assumed—I'm paraphrasing, of course—that it had formed.

The next line of questioning rested on a normal chemical procedure. For example, if you have ***XYZ-acetate*** *and you chemically remove the acetate, the resulting* ***XYZ-*** *could be considered "proof", albeit indirect, that the corresponding precursor in acetylated form had existed. So where does this get Mr. Fues?*

Q. I'd like to look at Juan Navia's November 5th deposition—Dr. Fraser Reid.

A. What page are we on?

Q. We are on page 195—at line 20:

"QUESTION: Okay.—the presence of these dichloro materials would indicate that the corresponding "dichloro acetates"*(i.e.* ***products #3 and #4)***—had been present at one time in the reaction"—"**You would have seen these in esterified form in the earlier step"**

Unfortunately Dr. Navia's reply was, to say the least, unhelpful! He replied: ***"If we did, I don't recall"***

Q. My question for you, Dr. Fraser-Reid, is [saying] that you don't recall something the same as [saying] that you were simply making assumptions?

A. No.

But does it really matter?

Q. I've got a question for you. If the inventors of the 463 patent had used dichlorinated standards in their—research—[they]—could have provided reliable information about whether **product #3** existed, right?

A. Yes.

Q. So you'll agree with Dr. Baker (*an expert on "our" side)* —that—if you had the **product #3** standard—that would have provided everything [that] a good analytical chemist would need to characterize the reaction mixture, right?

A. Yes, except my point was that I hadn't seen that those standards [had been] made—

Q. Just so we understand your testimony, Dr. Fraser-Reid—

A. Yeah.

Q. If the dichloro standards were available, they—would have provided you with sufficient information—to understand that the inventors had in fact accurately characterized their reaction mixtures, right?

A. Yes, if they had been made available, if they had existed, but I haven't seen any evidence that —**product #3**—is known—or was known at the time.

Q. –Dr. Fraser-Reid—you just asked about this issue. This is a memo that is dated July 19th, 1988?

JUDGE BULLOCK: Is this confidential or not?

MR. FUES: I'm sorry, we need to go on the confidential record, please.

Whereupon, the trial proceeded in confidential session that would last for the rest of the day.

Chapter 16
Thursday Night – It Was There All the Time!

After each day's hearing, the Bingham McCutchen attorneys, paralegals, and experts took the Washington Metro to the firm's offices. The line of limousines outside the courthouse were not waiting for us. At the firm's offices, we dined, buffet style, amidst intense discussion about how things were going for us, and for all of the Respondents in general. This was my first opportunity to review my cross-examinations by Messrs. Paulraj and Fues. I was worried about the goofs that I had made. My colleagues were reassuring, and suggested that I "lighten up."

Nevertheless, I questioned whether my case against the 463 patent had been successful, given the onslaught of Mr. Fues, jerking me around between my expert reports, my witness statement, and my deposition in search of inconsistencies. Had the court been convinced that the 463 patent was invalid because:

1. Preparation of the Vilsmeier salt in the presence of sucrose-6-acetate was an ***in situ*** operation that had been reported in the Mufti/Kahn patent 8 years earlier and therefore was not novel.
2. The chlorination of the sucrose-6-acetate was done by intermediate **A** (see Scheme 7.4) rather than by the Vilsmeier salt **B** as **required** by the 463 patent.

Perhaps the skillful Tate & Lyle lawyers had splattered so much confusion that the 463 patent had been given life-support.

Nevertheless, as I reflected on my day, I felt that something was not right, and I had 12 h to cogitate on this before returning to the witness stand on Friday morning. I had read all 19 pages of the 463 patent time and time again, but it seemed like a good idea to study them once more.

I decided to ignore the claims at the back of the patent. These had been thoroughly scrutinized by brilliant lawyers, on both sides of the dispute, and it seemed very unlikely that this organic chemist would discover some hidden nugget that had escaped them.

Instead I started at the front dealing with "Background of the Invention" which deals more with chemistry than law. *I had also read this section time and time*

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_16,

again, but strangely, the last paragraph of column 1, page 8 suddenly jumped out at me:

"The chlorination of **partially protected carbohydrates** is especially difficult because side reactions, such as **oxidation and elimination**, have a great tendency to occur".

I now had to get support for this piece of advice – and where better to start than the papers of Professor Hough, the inventor of sucralose? I had assembled a binder full of these, and I found what I wanted in *Sucrochemistry Part XII (Journal of the Chemical Society Perkin I, **1973**, page 1524–1528).* Indeed, there were convincing, cautionary examples.

In light of the inherent pending disaster, the seven free (i.e. *unprotected)* hydroxyl groups of the sucrose-6-acetate (Scheme 7.3) in the 463 patent, would have to be "*protected*" somehow.

The desired *protection* could be effected if ALL SEVEN of the OHs reacted with the Vilsmeier Reagent (**A** or **B** – it doesn't matter which) to give the **KEY COMPLEX** in Scheme 7.4. (The latter would actually consist of SEVEN O-chloroformimiun chloride salts).

My early intuition seemed justified. The "chemistry" was supportive – but what about the law? How about the patent itself?

First, claim 1(a) states:

"adding **AT LEAST seven molar equivalents** of an acid chloride to a reaction mixture—to form a chloroformiminium salt (*i.e. a substance such as **A** or **B**)"—.*

Why "**AT LEAST" seven**? This implied that there was a problem when fewer than seven were used.

This looked like the support that I needed from the patent itself.

I eagerly discussed my new insight with Gary Hnath our lead attorney. He was guarded in his enthusiasm; but he didn't discard it. I later realized that for this information to be presented to the Court, I would have to be subjected to redirect examination by Gary. But this was "new" stuff (kind of). Would that be admissable at such a late stage of the trial.

As I have stated above, chemists communicate by means of diagrams – or demonstratives as lawyers call them. I asked whether I could have a blackboard in the court room because it would be necessary for me to present another tutorial on Friday morning. Luckily Kinko's was right next door, and so an easel and chart paper were soon available for me to prepare my demonstratives.

I had already learned from my daughter and son-in-law that when lawyers go into the "trial mode", sleep disappears. My lawyer colleagues had been in this mode all week. They would be just getting down to business when I had faded at 1:00 am each night, and yet would be "as fresh as a daisy" when Court resumed next morning.

For this aging organic chemist, my trial mode was characterized by jitters and angst, and so on Thursday night (or more correctly Friday morning) at 1:30 am, I excused myself. I would either get some sleep or I would freak out.

Chapter 17
Day Eight of the Trial – I Return to the Witness Stand

17.1 Friday Morning February 29, 2008. A “Blackboard” Please

After the usual formalities, Gary began my re-direct examination. Judge Bullock’s courtroom was well-equipped with strategically placed TV screens, and Gary had arranged that the “Background to the Invention” section of the 463 patent would be projected so that all could see the following quotation:

“The chlorination of **partially protected carbohydrates** is especially difficult because side reactions, such as **oxidation and elimination**, have a great tendency to occur.”

The highlighted words had to be decoded for the audience, and that is what I hoped to do with my demonstratives. The easel was brought in. Judge Bullock’s sight-line was of paramount importance and so lawyers and other interested parties had to form concentric rings as I reverted to the old fashioned practice of using a ‘blackboard.’

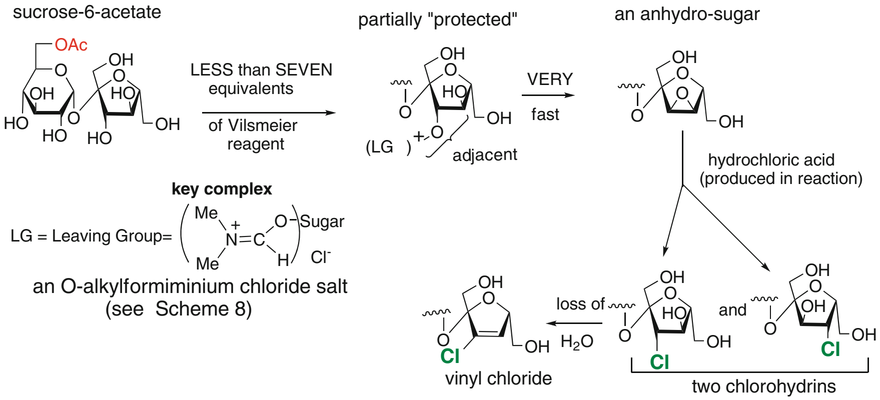
BY MR. HNATH:

Q. And, Dr. Fraser-Reid, just refer to [the demonstrative] numbers with your explanations, please.

A. “All right. In [Scheme 17.1]—the “partially protected” structure—[represents]—the situation where you have a free hydroxyl group—adjacent to the leaving group—the “leaving group” [is] my abbreviation for the o-alkylforminium ion (compare KEY COMPLEX, Scheme 7.4)—[the free] hydroxyl would displace [the leaving group] leading to [the] three-membered ring with the oxygen, —an anhydro sugar, as we call it.

“Now—once you form the anhydro sugar—that opens up a whole world—hydrochloric acid [is] a by-product of the [Vilsmeier] reaction. This [anhydro sugar] would open up —[by the action of]— hydrochloric acid, to give chlorohydrins, in which you have a hydroxyl group adjacent to a chlorine. Further reaction could go, for example,—with expulsion of water to give you a vinyl chloride—

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3_17, © Springer-Verlag Berlin Heidelberg 2012



see: Ballared, **Hough,** Richardson and Fairclough, *J. Chem. Soc., Perkin Trans. I,* **1976**, 1524

Scheme 17.1 Problems with chlorination of partially protected carbohydrates

"There is the anhydro sugar, Your Honor. There is the vinyl chloride (see Scheme 17.1)"

Q. And when you say, "there," just for the written record, could you tell us what you're referring to, please?

A. So from just one epoxide (*i.e. anhydro sugar*) you have obtained three subsequent derivatives. And — that's on the five-membered ring of the sucrose. The situation gets much worse over here (*i.e. the six-membered ring)* because you have three adjacent — hydroxyl groups that can [*react with the Vilsmeier reagent*]. And in fact, the problem of working with **partially protected** sugars was addressed in the '463 patent in column 1 on the—very last paragraph of column 1."

Q: Could we pull that up (*on the screen)*, please? Just briefly, Dr. Fraser-Reid, can you tell us what you're referring to?

A: I will. Here we are *(reading from the patent itself)*:

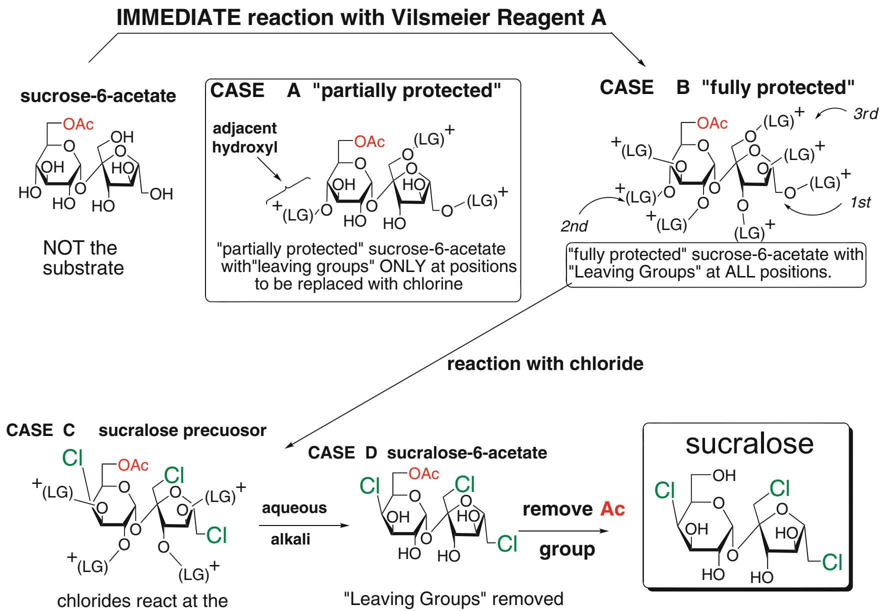
"The chlorination of **partially protected carbohydrates** is especially difficult because side reactions, such as **oxidation and elimination — have a great tendency to occur.** (emphasis added).

The unfortunate thing is that the patentees did not realize that they were in fact dealing with **fully protected carbohydrates** — because, if only some of the hydroxyl groups had formed O-alkylformiminium chlorides, the molecule would be partially protected, and would be destroyed.

"What you want to—is **not** have any free hydroxyl groups. You want it fully protected, and — in this case — the O-alkylformiminium salt [would] offer protection."

Q. And, Dr. Fraser-Reid, how then does all this support your position concerning Claim 1of the '463 patent?

This question by Mr. Hnath gave me the opportunity to examine questions that were presented graphically in a second demonstrative (Scheme 17.2). What is the substrate that actually undergoes chlorination? And is it Sucrose-6-acetate as the



Scheme 17.2 Choices for sucrose-6-acetate

patent states? If the Vilsmeier reagent formed adducts ONLY at the three positions where chlorines are to be installed (i.e. ***CASE A****) there would be an adjacent hydroxyl – as indicated. But if adducts were formed at ALL SEVEN positions (i.e.* ***CASE B****), there would be absolutely NO adjacent hydroxyls, and the dire problems depicted in Scheme 17.1 would not occur.*

Nevertheless, the “expected ease of replacement” would remain the same at the three desired positions.

A. —that is why — at least seven molar equivalents are needed, Your Honor. I mean, we’re running a business here. If you only need three [hydroxyls] to be displaced by chlorine, why are you —using seven *equivalents*? Obviously, the experimental results for the patentees [must have shown] that you need all seven, [so that]–you don’t –have– any unprotected hydroxyl groups.

Q. Could we look at the Sankey deposition transcript, page 68, line 1? And I’ll read it into the record:

“QUESTION: Okay. So as I understand it, you’re starting with the sucrose-6-acetate, which blocks the 6 position, is that right?”

“ANSWER: Yes.”

“QUESTION: Then this Vilsmeier intermediate goes on the seven available hydroxyl groups, the ones that are not being blocked?”

“ANSWER: That’s what we think happens, yeah.”

“QUESTION: And then these positions have different reactivities—is that correct?”

"ANSWER: Yes."

"QUESTION: So what then, as you understand it, Doctor, happens as you heat up the mixture—?"

ANSWER: As you heat it up, the most reactive position reacts first and so on, until you substitute the three activated groups."

BY MR. HNATH:

Q. Does this support your position, Dr. Fraser-Reid?

A. I could not have said it better myself.

17.2 Return of the "Office Action"

Why did I believe that Scheme 17.2 would be such a strong challenge for the 463 patent? For the answer, we must go back to the Office Action (see Chap 7.4.3). *The charge of lack of novelty was refuted in the very first sentence as follows:*

"The invention described and claimed in the above identified application relates to an improvement in the process for ***chlorinating sucrose-6-[acetate] using a*** *[Vilsmeier* ***salt] as the chlorinating agent"***

But Scheme 17.2 shows that technically, the substrate that is chlorinated is NOT sucrose-6-acetate, but the fully protected analog ***CASE B****.*

From the standpoint of chemistry this, again, would not be a significant difference. But from the law's standpoint, given the narrow window of the patent's novelty, and hence its related validity, the specter of infringement seemed less and less threatening.

Mr. Hnath's re-direct examination now moved to the "controversy" in my version of the Vilsmeier Reaction in Scheme 7.4.

BY MR. HNATH:

Q. Okay. You discussed yesterday the — intermediate *(i.e. structure* ***A****, Scheme 7.4).* Can the — intermediate be considered a salt?

A. Yeah, it's a soluble salt.

Q. In what sense is it a salt?

I had to explain that a "salt" normally has positve (+) and negative (−) entities and is frequently solid.

A. —[But]—our bodies are full of [soluble] salts, for example, in our knees—the synovial fluid in the knee is chondriotin sulfate, and it's a soluble salt.

This issue gave me the opportunity to say something about the seven adjacent positively charged groups in ***case B*** *(Scheme 17.2)****.*** *When I suggested this early on, experts on both sides of the litigation had opposed the idea, saying that the seven positive charges would repel each other. However, Professor Eric Walters, the other expert on our team, was supportive. He provided a rationalization which he kindly agreed to let me use. Accordingly, I told the court that the human body is full of DNA which has thousands of clusters of negatively charged phosphate units, which should also experience electrostatic repulsions.*

But our bodies do not disintegrate because of DNA repulsions between the negative charges, and this is because the our bodies are full of water which is a polar solvent i.e. has (+) and (−) "domains". The water positions itself around the negatively charged phosphates thereby defusing any repulsive tendencies.

Similarly, the solvent for the chlorination reaction, dimethylformamide (DMF), is also a polar solvent and would position itself to prevent repulsions.

BY MR. HNATH:

Q. Before we leave the demonstrative, Dr. Fraser-Reid, could you label the pages of the demonstrative, please, for the record, so we'll have some kind of a title, the drawings you made on the easel?

JUDGE BULLOCK: Do you have a suggestion, Counsel?

MR. HNATH: Why seven groups are required.

MR. FUES: Objection, leading.

JUDGE BULLOCK: We're just trying to do an administrative matter here.

MR. HNATH: Right.

THE WITNESS: The need for complete — well, that's probably too much.

JUDGE BULLOCK: What about something like Dr. Fraser-Reid's demonstrative on redirect examination, something like that? I don't want to spend too much time.

I have to thank Judge Bullock for suggesting the names for the Schemes 17.1 and 17.2

MR. HNATH: Sure, that would be fine.

THE WITNESS: That would be fine.

JUDGE BULLOCK: Is that agreeable? All right.

My re-direct-examination by Mr. Hnath continued, and he now turned to another contentious issue that Mr. Fues had pummeled me about concerning the Navia deposition. This was the likelihood of ***product #3*** *in Scheme 7.3.*

BY MR. HNATH:

Q. You were asked yesterday about the Navia transcript that you had reviewed before your deposition. Let me put upon the screen Dr. Navia's transcript from November 5th, 2007. And go to page 157, line 23. And I'll read it in to the record.

"QUESTION: "And — what are the multiple dichloros that can be formed?"

There's an objection from Mr. Fues.

Remember Mr. Hnath is reading from Dr. Navia's deposition, and so objections are really only pro forma.

ANSWER: "For example, we know that chlorination occurs mainly at 4 on the glucose and the two primary positions on the fructose, 1' and 6'. One can generate — three."

"QUESTION. Okay. And which two are being referred to here?" *(in the patent).*

"ANSWER: I don't know."

"QUESTION: Could you look at the abstract to the patent?"

"ANSWER: I don't see any indication here, — that the various dichloros (*were*) identified, so I don't know from the data."

"QUESTION: Would someone have made that analysis at some point as to which dichloros were corresponding to these peaks?"*(presumably in a spectrum)*

"ANSWER: "Yes, at some point."

"QUESTION: And what kind of documents would there be that would help us in determining which dichloro species corresponded to these peaks?"

"ANSWER: —we weren't interested in their particular identity, so we would not have bothered to identify these particular peaks."

"And — and in my recollection, I don't think we ever did take the trouble to do that." (*emphasis added).*

Dr. Fraser-Reid, does it —

The judge interupts:

JUDGE BULLOCK: I'd caution you, whatever question you have, to be sure not to phrase it as a leading question.

BY MR. HNATH:

Q. Does this support or not support the testimony you gave yesterday?

A. Yes, because —

JUDGE BULLOCK: I'm sorry. That was an either or, support or not support.

A. "Sorry. Yes, it supports the testimony that — there was no evidence of the 1'-6' ***(product #3)*** having been formed. And as a carbohydrate chemist, Your Honor, I was particularly interested in that because in my own lab I had tried to make a 1' derivative and found it was very difficult.

"I know Dr. Navia, and when I saw the work I said—this is very reputable work because I have known him from when he was a post doctoral student."

BY MR. HNATH:

Q. And, Dr. Fraser-Reid, is this testimony that you had personally reviewed before your deposition?

A. Yes, I did.

Q. So were you relying only on attorneys' representations *(as Mr. Fues had insinuated yesterday)*—

A. No.

Q. — on your transcript or had you read it yourself?

A. Oh, no, I read it.

(Whereupon, the trial proceeded in confidential session.)

OPEN SESSION

Mr. Hnath's re-direct-examination continues. He now takes aim on another insinuation from yesterday.

BY MR. HNATH:

Q. Okay. Dr. Fraser-Reid, I want to put up on the screen a portion of your deposition that Mr. Fues asked you about yesterday—which I'll just read into the record, so it's clear:

"QUESTION: Based on your 47 prior years of experience, did you think that ***product #3*** was formed below 85 degrees?"

"ANSWER: Well, I would have said, yes, because, if it's formed in the '463, there's no reason it shouldn't form in Mufti, with that as precedent."

And then the following question and answer, which Mr. Fues **didn't** read, were given *(emphasis added)*:

"QUESTION: And relying on anything else?"

“ANSWER: No, only that precedent, which I found stunning.”

BY MR. HNATH:

Can you explain what you meant, by that, “which I found stunning”?

A. Well, as I said, my 47 years to which Mr. Fues referred means — I would not have believed that the 1’-6’ would form below 85 degrees, but when I saw it in the patent, I said, well, I guess I am wrong. And in fact —at one stage— I think I said to Mr. Fues, — if I could have that authenticated—I would probably write a paper about it because I tried to make it and couldn’t.

Q. What happened when you tried to make it?

A. It just wouldn’t go. It’s very stubborn. I wasn’t working at high temperatures, I may emphasize.

Q. Could you next look at RX-168? Turning to a different topic. Mr. Fues asked you questions about —

Mr. Hnath’s redirect examination now turns to questions about tin chemistry which I had been asked during my cross-examination by Mr. Fues. But I cannot report about this matter, because:

MR. HNATH: And I think, Your Honor, this will be confidential to GDFII

JUDGE BULLOCK: On the confidential record.

Whereupon, the trial proceeded in confidential session that lasted the rest of the morning, after which I was excused from the witness box.

The afternoon session was devoted to legal wrangling, with the lawyers and Judge Bullock making sure they ended on the same page. When they had finished, everyone breathed a sigh of relief, excepting the busy-as-a-bee lawyer:

MR. GOULET: One last matter, and this is on the exhibit list—[do] you require filing of the stipulation or if merely moving it into evidence is sufficient?

JUDGE BULLOCK: Moving it into evidence would be fine.

MR. GOULET: Thank you Your Honor.

NR. HNATH: Your Honor, I just wanted to say thank you for this, your attention to this matter and your Staff and your courtesies over these last two weeks, and these are very busy times, and certainly everyone’s cooperation has made it easier for everybody, so I wanted to say thank you.

JUDGE BULLOCK: Thank you.

MR. JARVIS: And, Your Honor, on behalf of Complainant, Tate & Lyle—[we]—recognize the contributions of the Commission, beginning with the Staff, the judge’s office, and general counsel to make this an impartial and livable dispute resolution mechanism, and I think everyone on both sides of the aisle shares that.

JUDGE BULLOCK: Thank you, And—I really appreciate the spirit of cooperation, and—a lot of issues that looked like we were going to spend a lot of time [we were able] to work it out and—meet our deadline of finishing today.

I’d also like to thank our reporter for her excellent work and patience, and I’m impressed by the fact that you were able to get all these chemical names right.

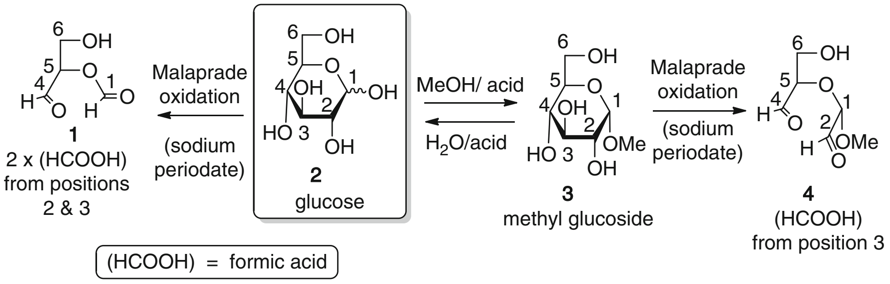
(Whereupon, at 3:45 p.m. the trial was adjourned.)

Appendix A: 1958 Chlorination of Sucrose Products Isolated by Jones/Bragg

Today, structure determination of the products obtained by Phil Bragg by chlorinating methyl glucoside and sucrose (see Sect. 3.1.6) could be accomplished in a matter of hours by the use of Nuclear Magnetic Resonance (NMR) spectrometry. But in 1958 this technique was still in its infancy, and so Phil resorted to the Malaprade, or periodate oxidation.

(Nuclear Magnetic Resonance is the science behind MRI {Magnetic Resonance Imaging} that is widely used today for medical diagnosis. The word "nuclear" was apparently dropped lest worrisome patients envisage a mushroom cloud).

The enabling feature of the Malaprade oxidation is that the bond between contiguous hydroxyl groups is cleaved. Thus in the case of glucose **2**, (Scheme A1) there are three sets of contiguous hydroxyl groups (between positions 1&2, 2&3, and 3&4). Each would be cleaved, and positions-2 and −3 would be excised as HCOOH (formic acid).



Scheme A1 Malaprade (Periodate) oxidation technology

NOTE: The formyl ester in **1** is easily cleaved, and so caution during work-up is recommended, since its hydrolysis would give a third mole of formic acid.

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In the case of methyl glucoside, **3**, there are two sets of contiguous-OH groups (between positions 2&3, and 3&4), so only one HCOOH (formic acid) would be produced, resulting from position-3.

The number of formic acids released when periodate oxidation occurs, is therefore an indication of the number of contiguous hydroxyl groups in the sample:

0 formic acid = 1 set of contiguous OH groups
1 formic acid = 2 sets of contiguous OH groups
2 formic acids = 3 sets of contiguous OH groups

Helferich's 1921 analysis of the major product that he had obtained from methyl glucoside had established that two of the hydroxyl groups had been replaced by chlorines. He obtained compelling evidence that one of these was at position-6. Assuming that he was correct, the options for the product obtained by Bragg were **5**, **6** or **7** the second chlorine being at position-2, 3 or 4 respectively (Scheme A2).

When Bragg subjected his product to Malaprade oxidation, there was (a) a reaction – but (b) no HCOOH was released, which meant that there was one set of contiguous hydroxyl groups. This information therefore ruled out **6**, and so Bragg was down to **5** or **7** (Scheme A2).

Boiling **5** with acid would give hemiacetal **8**, which upon Malaprade oxidation would give **9** - *without* liberation of HCOOH.

By contrast, boiling **7** with acid would give hemiacetal **10**, which upon Malaprade oxidation of would give **11** - with liberation of one equivalent of HCOOH. This result was observed, therefore the chlorination "product" MUST be **7**, rather than **5**.

The second chlorine was therefore at position-4; but the squiggly line in **7** means that the chlorine could be "up" or "down".

For the final piece of the puzzle, Bragg was fortunate that compound **12**, with a "down" chlorine at position-4, had been prepared previously. He therefore subjected **12** to the action of sulfuryl chloride, in order to install chlorine at position-6, thereby obtaining compound **13**.

Compound **13** was NOT identical to the product obtained from reacting methyl glucoside with sulfuryl chloride.

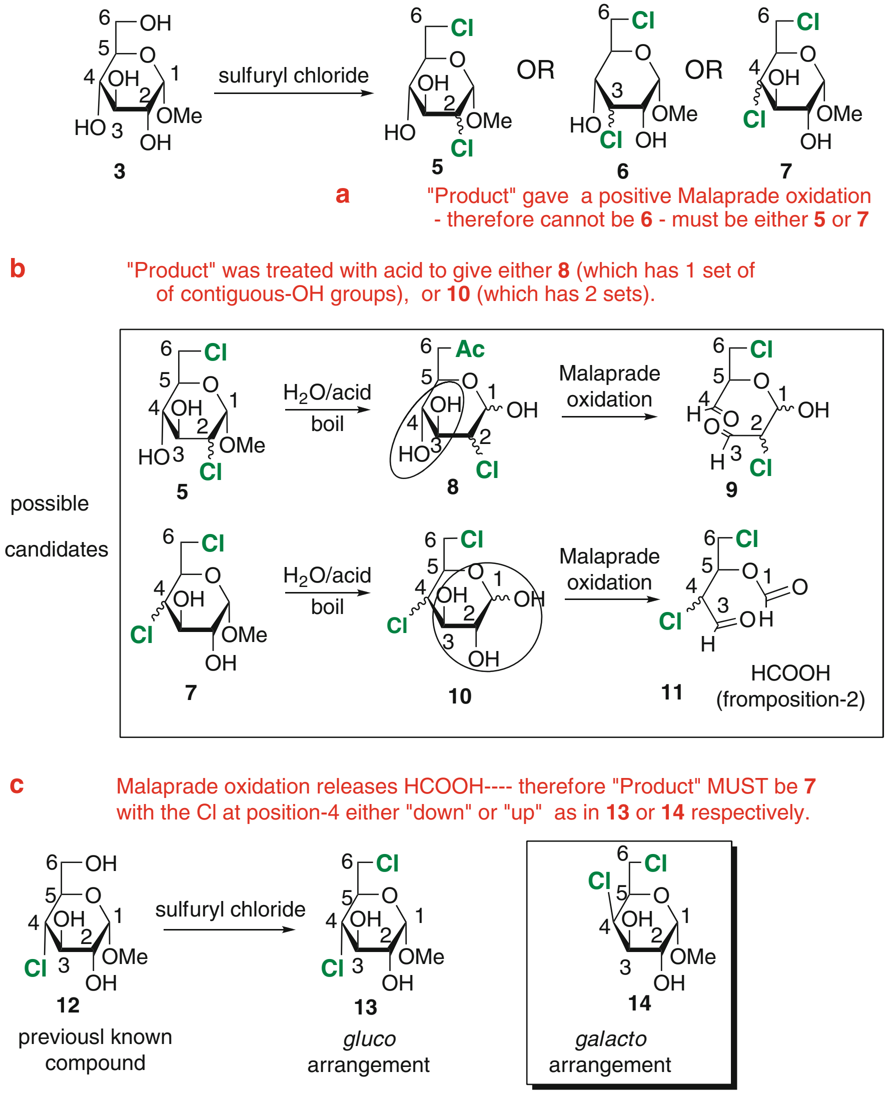
Bragg's product must therefore be **14**.

This result meant that in the reaction with sulfuryl chloride, position-4 had been inverted; i.e. the sugar had been changed from a *gluco* derivative ("down" at position-4), to a *galacto* analog ("up" at position-4).

The results of Bragg's work were published in a paper entitled "The Reaction of Sulfuryl Chloride with Glycosides and Sugar Alcohols. Part I" in the *Canadian Journal of Chemistry* volume 37, **1959**, 1412, the authors being P. D. Bragg, J. K. N. Jones and J. C. Turner [1].

This paper completed the work that Helferich had begun (Berichte volume 58, **Helferich et al. 1925**, 886 [2]), and constituted the first thorough study of the reaction of a sugar with a chlorinating agent.

Sucrose is a glucoside derivative as is obvious from a comparison of structures **3** and **15**. Chlorination should therefore be similar in the *gluco* (six-membered ring)



a "Product" gave a positive Malaprade oxidation - therefore cannot be **6** - must be either **5** or **7**

b "Product" was treated with acid to give either **8** (which has 1 set of of contiguous-OH groups), or **10** (which has 2 sets).

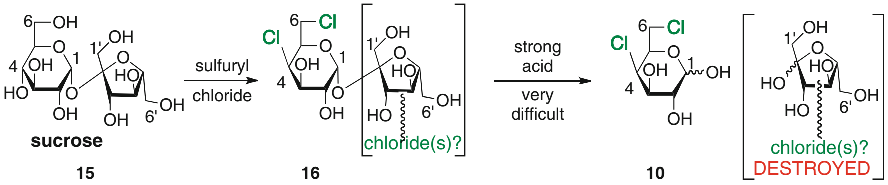
c Malaprade oxidation releases HCOOH---- therefore "Product" MUST be **7** with the Cl at position-4 either "down" or "up" as in **13** or **14** respectively.

d Chlorination of known **12** gave **13** which was different from the "Product" Therefore the Product" must be **14**

Scheme A2 "Product" from chlorinating methyl glucoside (**3**) is **5**, **6**, or **7**

domain. Indeed this proved to be the case as was substantiated by obtaining the hydrolysis product **10**.

It is seen from Scheme A3 that cleavage of the intersaccharide bond of **16** was so demanding, that the fructose moiety was destroyed in the process. This observation by Jones and Bragg foretold the future history of these compounds. Sucrose itself, is



Scheme A3 Exploratory study for chlorinating sucrose

very prone to acid hydrolysis, so one of the chlorines introduced was clearly impeding the hydrolysis. The position of the responsible chlorine is not known at present, but position 1' is the most logical, based on the armed-disarmed principles that the author has advanced [3].

However, the difficulty in acid-hydrolysis foretold the parallel difficulty in enzyme-catalyzed hydrolysis, which is responsible for the success of the material as a non-caloric sweetener (see Fig. 5.2).

References

1. Bragg PD, Jones JKN, Turner JC (1959) Can J Chem 37:1412
2. Helferich B, Sproek G, Besler E (1925) Berichte 58:886
3. Fraser-Reid B, Lopez JC In "Reactivity Tuning in Oligosaccharide Assembly" Chapter 1 Springer, Heidelberg, 2011

Appendix B: A Perfect Storm of Accidents

An "Accident" in Canada

The evolution of the sucralose (SPLENDA) story once again emphasizes the uncanny coincidences of luck, serendipity and chance in science – and arguably in life.

Sucrose, **1**, has eight OH (hydroxyl) groups; but it is obvious from Jones' work in Scheme A2 that they have different reactivities since, upon treatment with sulfuryl chloride, only some were replaced with chlorine. Hough's first 15 papers, *Sucrochemistry* Part I to Part XV, can be viewed as a familiarization reactivity tour of the sucrose molecule.

This familiarization notwithstanding, the first preparation of sucralose, was not launched with one of their own exploratory compounds, but with a compound that had been prepared 15 years earlier by Canadian scientists McKeown and Serenius, in Hayward's lab at the University of British Columbia.

Hayward and co-workers had prepared compound **6** accidentally. They had treated sucrose with triphenylmethyl (trityl) chloride in the cold so as to derivatize the primary sites only as shown in the desired material, **2**. Trityl groups, shown in blue, are known to be very sensitive to acids. Acetylation then added five acetyl protecting groups (the red Acs) at the secondary positions, giving **3**. The Canadian chemists then subjected the latter compound to acid treatment in the expectation that the blue trityl would be removed, leaving three primary-OH (hydroxyl) groups, as in **4**. They did indeed get three-OH groups, but as shown in **6**. This meant that the acetyl ester at position-4 had migrated to position-6, most likely via the orthoacid **5** shown in brackets in Scheme B1, leaving the free-OH at position-4.

(*Younger readers should know that when this work was done, the mechanism of functional group migration was still under investigation*)

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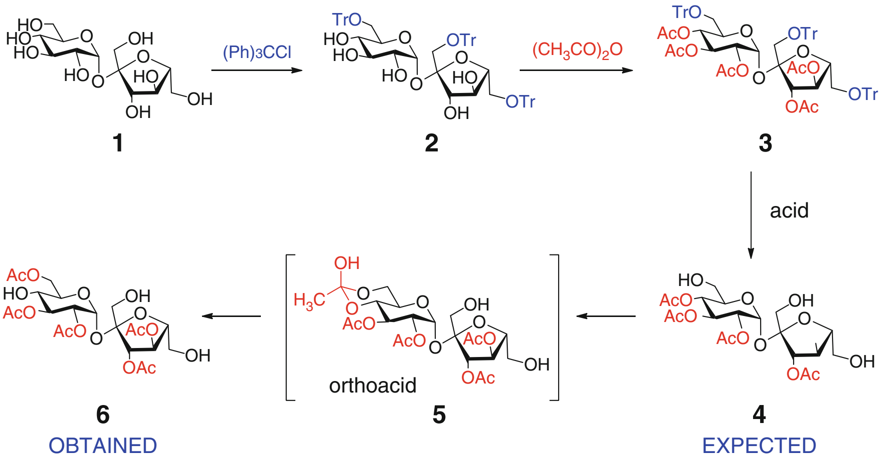
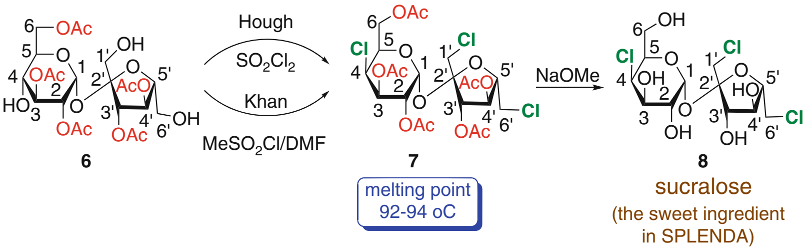


Scheme B1 A critical development



Scheme B2 One good accident deserves another

An "Accident" in England

Hayward's 15 year old Canadian discovery was put to use by Hough's co-workers. Thus, in *Sucrochemistry* Part XVI, which was submitted for publication in September 1974, but appeared in 1975, Hough's group reported that chlorination of compound **6** with sulfuryl chloride gave a 67% yield of compound **7** (Scheme B2). The five red Ac protecting groups were then removed to give compound **8**.

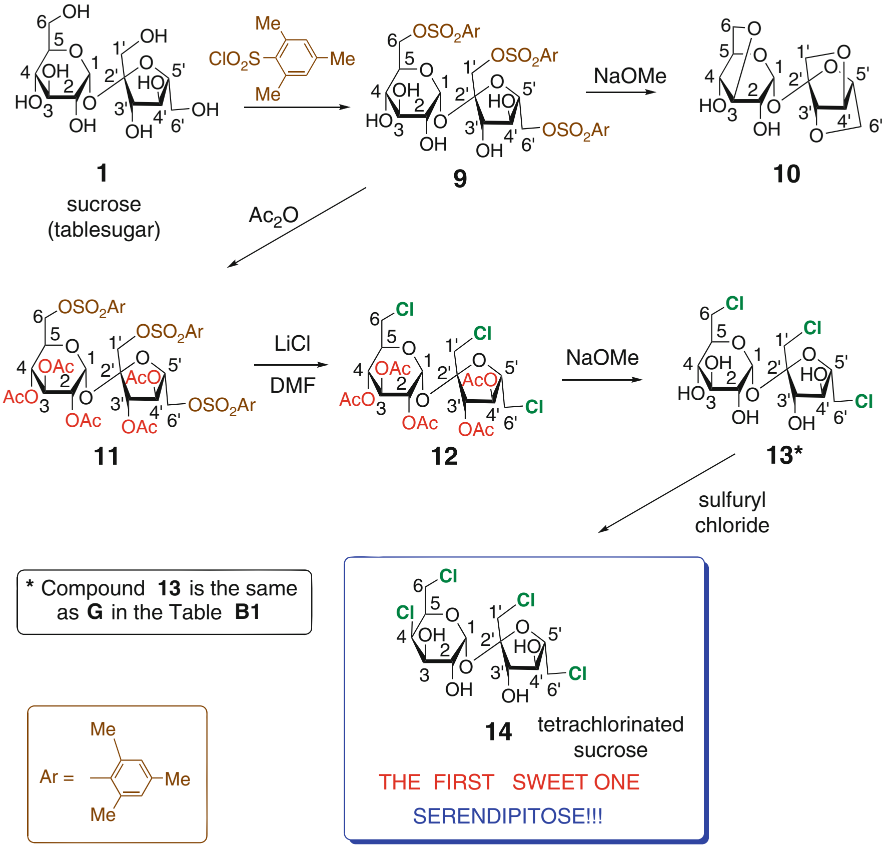
The melting point of intermediate **7** is emphasized in Scheme B2, because this compound would prove to be useful in later commercial preparations of sucralose.

Compound, **8**, is now known as sucralose; but the paper made no fanfare or drum roll to announce its discovery. Indeed, the paper shows clearly that Hough's group was more interested in replacing the chlorines so as to obtain various (more interesting?) derivatives of sucrose, as is apparent from the paper's title: "Derivatives of β-D-fructofuranosyl α-D-galactopyranoside".

Many names were given to compound **8** including “1,6-dichloro-1,6-dideoxy-β-D-fructofranosyl-4-chloro-4-deoxy-α-D-galactopyranoside”, and “4,1’,6’-trichlorogalactosucrose” (TGS). The name “sucralose” was given after the collaboration of Tate & Lyle and McNeil Specialty Chemicals to commercialize the product. The collaboration gave rise to the formulation of SPLENDA, which consists of 1% of sucralose in maltodextrin.

Hough and his coworkers had been developing methods for replacing OH (hydroxyl) groups of sugars with chlorine, using methods that did not employ the harsh sulfuryl chloride, that had been used by Jones. The approach they used bore the imprint of A. C. (Dick) Richardson, Hough’s second-in-command. As a young scientist, Richardson had developed a thoughtful, well-regarded theory to rationalize the sort of selective reactions of sugar-OH groups that had been observed by Jones.

Direct replacement of an OH group by Cl is difficult, and so the process needs help. Sulfonylation with methyl or p-tolyl sulfonyl chlorides is popular for



Scheme B3 Sweeter than sucrose – but not sucralose esterifying hydroxyl groups and thereby improving their leaving group ability. In this context, an excellent protocol was derived from Guthrie's report that treatment of sucrose with mesitylsulfonyl chloride gave higher yields of the 6,1',6'-trisulfonate, **9**, (Scheme B3) than the methyl or p-tolyl analogs. This selectivity can be compared with the selectivity of the tritylation process **1** → **2** in Scheme B1.

Hough and co-workers acetylated **9**, presumably to prevent intramolecular displacements which could result in formation of cyclic ethers (e.g. anhydro rings such as those in **10**). Pentaacetate **11** was then treated with lithium chloride to give **12**, which could be deacetylated to trichloride **13**. (Notably, the latter is the same as structure **G** in the Table below (Table B1); it was not very sweet). Subjecting trichloride **13** to the standard reaction with sulfuryl chloride, resulted in chorination at C4, with inversion, to give **14** the first chlorinated sucrose that was "tasted" by Shashikant Phadnis. (See Chap. 4 for details).

And here issues of fate, luck, serendipity and destiny become intertwined.

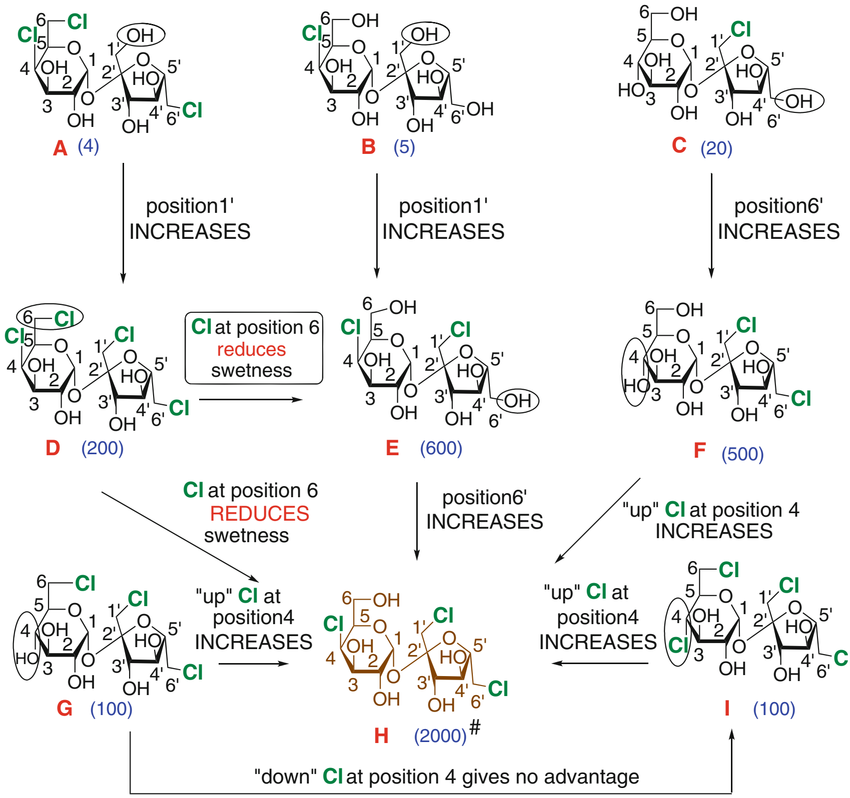
Wikipedia reports that [on] a late summer day, Phadnis was told to test the powder. Phadnis thought that Hough asked him to taste it - so he did."

This account is not entirely accurate. The "test versus taste" story as recalled by Professor Hough and Drs. Riaz Khan and Shashi Phadnis is outlined in Sect. 4.1.5.

However, Phadnis' "taste" resulted in patents being filed. Patent 1,543,167 (Application No: 616/76) was filed by Tate and Lyle Limited, on January 8, 1976 which dealt with the sweetness of chlorinated sucroses. The Inventors were Khan, Hough, Phadnis and Jenner, and the assignees were Talares Development based in Curacao, Netherlands Antilles (aka Dutch West Indies) a subsidiary of Tate & Lyle. The very same day (8 January 1976) Khan, Hough and Phadnis filed patent No 1,542,168 dealing with the synthetic approach to chlorinated sugars. The Inventors were the same with the exception, that Jenner was dropped. The Assignee was the Research Corporation, New York.

Tested by Professional Tasters (or Tasted by Professional Testers?)

Table B1 Analysis of sweetness of chlorinated sucroses (Numbers in blue show sweetness of compounds **A** to **I** relative to sucrose)*



comparing two structures with only ONE difference

(a) A → D & B → E show that Cl at position-1' INCREASES sweetness

(b) C → F & E → H show that Cl at position-6' INCREASES sweetness

(c) F → H, I → H & G → H show that "up" Cl at position-4 INCREASES sweetness

(d) D → H & D → E show that Cl at position-6 DECREASES sweetness

(e) comparing G & I shows that "up or down" Cl at position-4 has same effect

\# This value was subsequently revised to 600

---

*Values taken from Tate & Lyle patent # 1,543,167 (arrows point to change in sweetness when the encircled group is replaced)

Sucralose is Identified

The patent evaluated the sweetness of the nine chlorinated sucrose derivatives (**A** to **I**) shown in Table B1, the associated numerical values, shown in blue, being the sweetness relevant to sucrose. These sweetness levels were determined by a professional tasting panel, whose tongues were, presumably, more sophisticated than Phadnis'. (The commonly accepted value is that sucralose is 600 sweeter than sucrose. However, as shown in the Table, the value in the Tate & Lyle patent is 2000 sweeter. The value was evidently revised after the patenting).

In the Table, for each structure, with the exception of **H**, one functional group is encircled. This group is changed in the direction of the arrow. For example in **A**→**D** position-1' is changed, and in **E**→**H** position-6' is changed.

Items (a), (b) and (c) in the summary at the bottom of the Table indicate increases in sweetness that occur when a single functional group is changed. By contrast, item (d) shows that Cl at position 6 causes a substantial decrease in sweetness.

On the other hand, a change in the "down" orientation at position-4, i.e. inserting chlorine with retention of configuration, **G**→**I**, has no effect – positive or negative.

The Table raises a wealth of interesting observations:

- The single chlorine at position-1' makes structure **C** 20 times sweeter than sucrose
- Chlorine in the "up" orientation at position-4 of structure **B** increases sweetness over sucrose fivefold

Let us therefore put chlorines at both positions-1' and "up" at position-4, thereby obtaining structure **E**. It is seen that the sweetness enhancement is much bigger than the cumulative (i.e. 5 + 20), or multiplicative (i.e. 5 x 20) results, the value being 600 times sweeter than sucrose.

The two chlorines therefore seem to have a synergistic effect.

If we go from **C** to **F**, the importance of position-6' for enhancement of sweetness is suggested

Therefore, when we go from structure **E** to **H** where only position-6' is chlorinated, sweetness increases more than threefold.

On the other hand, addition of chlorine at some sites can have a negative effect. Thus compare structures **D** and **H**. REMOVING the chlorine from position-6 increases sweetness in **H** by a factor of 10. Or put another way, the chlorine at position-6 of **D** negates the synergistic effects of the chlorines at positions-4, 1' and 6' in structure **H**.

Contribution of the substituent at position-4 invites comment. Comparison of structures **G** and **I** show that replacing the "down" OH with a "down" chlorine has neither a good nor a bad effect. However, comparing **D** and **I** shows that the "up" chlorine gives a positive enhancement.

Appendix C: Some Are Sweet; Some Are Not

The Concept of A "Glucophore"

The data on the chlorinated sucroses listed in the Table B1 are excellent for scientists who study the sweetness phenomenon. The various chlorines clearly contribute to, or detract from, sweetness, and disentangling their contributions presents an engaging puzzle.

In this adventure, attention must be drawn to a pioneering theorist in the study of sweetness, the late Professor Robert Shallenberger of the New York State Agricultural Experimental Station, who published a seminal theory 50 years ago. It is not possible to include Shallenberger's theory in this chapter; but an excerpt from Professor Hough's 1986 opinion in a lecture entitled the "The shape of sweeteners to come" summarizes early approaches of the theory.

"Protein molecules are ideally suited to form pairs of hydrogen bonds, as they have amide (N–H) and carbonyl (C=O) sites strategically placed about 0.3 nanometers apart. The carbonyl group (C=O) is seeking a hydrogen on another atom, and the amide group (N–H) is seeking an atom rich in electrons. A molecule that has these complementary sites, which we call **AH** and **B** respectively, 0.3 nanometers apart, can bind the protein. If the protein forms part of the taste receptor at the tip of the tongue, the brain receives a signal saying that a sweet taste is present.- - - - - [Subsequently] - - - - Lemont Kier - - - studied sweet molecules - - - [and] - - - noted that most of them shared a third common factor - part of the molecule was hydrophobic, in other words repellant to hydrogen bonds. He called this the **X** site. The whole molecular arrangement, the triangle of sweetness, is called the "glucophore". A version of the Sweet Triangle is given in Scheme C1.

In light of the theory, an enthusiast might attempt to contort the chlorinated sucroses (see Table B1) and the artificial sweeteners (Sect. 5.1.4) so as to form a "sweet triangle" with the bonds corresponding to the **AH** and **B**, and hydrophobic domains, all of which are depicted in Scheme C1. This would be a major challenge, given the number of hydroxyl groups on the chlorinated sugars. A molecule would

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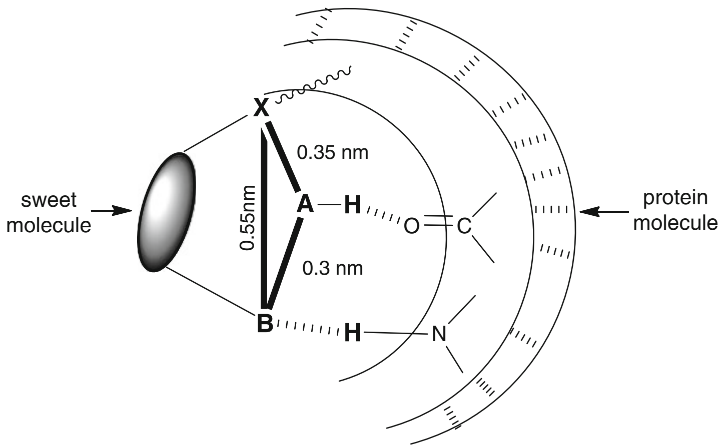


Scheme C1 The sweet triangle

have to be twisted into itself in such a way that the hydroxyls were all pointing inwards.

However, these 50-year old concepts have been overtaken by sensory analysis, according to which sweetness is only one variable. Thus the human tongue “can detect and discriminate between sweet, bitter, sour, salty and umami (savory)” (see Sect. 5.1.3). A layman, such as the writer, might have expected that, during evolution, each of these five detection “zones” would have staked out its individual territory on the tongue. However the analysis as discussed in Sect. 5.1.3, indicates that all five sensory share the same space!

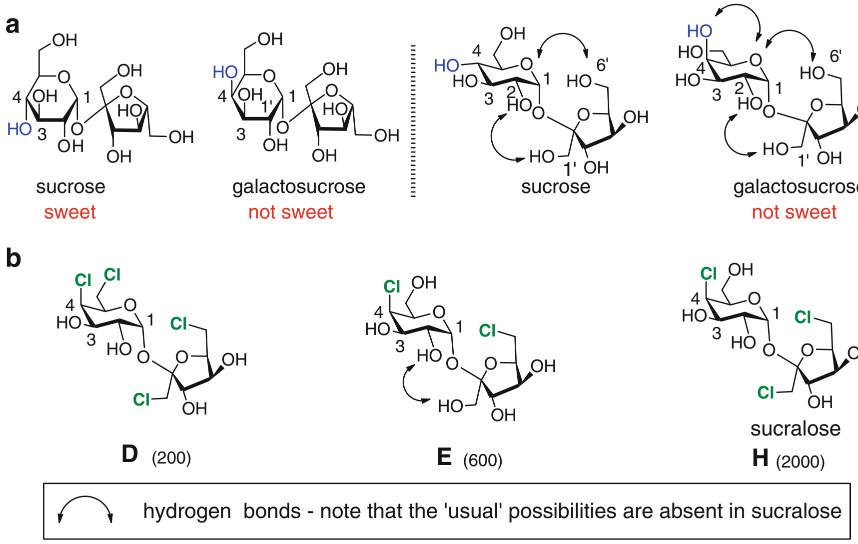
Of course, such a superficial analysis is indeed superficial. For example, “taste pores” on the surface of the tongue provide access to labyrinthine neural networks beneath the tongue’s surface. Decoding these pathways is one of the challenges for sensory scientists.

Furthermore, an added complication comes from challenges to the notion of five taste centers. As an alternative, taste modalities are thought to be spread over the entire surface of the tongue.

While we wait for resolution of these conflicting theories, an example from structural chemistry is notable.

The Orientation at Position-4 Is Clearly Important

In his 1976 lecture to an American Chemical Society Symposium, Professor Hough first suggested that position-4 of sucrose is somehow unique. He began by comparing sucrose and galactosucrose as shown in Scheme C2(a). The only difference between them is the orientation of the hydroxyl group at position-4. Hough notes that sucrose is sweet, but galactosucrose is not.



Scheme C2 Sucrose versus Galactosucrose

Why? Why not?

Does the answer rest in how we visualize the sugar? In this connection, it is helpful to revise how the structures are drawn. In the drawing of the molecules in the left-hand-side of Scheme C2(a) the glucose moiety of sucrose is presented in the “the Haworth projection”. It appears from this projection that the hydroxyls at positions 3 and 4 are “far apart”.

By contrast the (conformational) drawings on the right-hand-side of Scheme C2 (a), which are intended to be an approximation of how the molecules look in Nature, show that the hydroxyl groups at positions 3 and 4 are close.

In addition, the double arrowheads indicate that hydrogen bonds can exist between the C2-OH of gluco and Cl′-OH, and the glucose ring oxygen and C6′-OH. Notably, galactosucrose has an additional hydrogen bond, between the axial C4-OH and the ring oxygen, that does not exist in sucrose.

These interactions constrain the molecule’s movements. Dose that affect sweetness?

However, note that the C4-OH in both compounds, “points” in different directions. In sucrose, it is equatorial (i.e. points away from the molecule), while in galactosucrose it is axial (i.e. points “up” over and above the molecule).

Does this mean that an axial group at C4 of sucrose inhibits sweetness?

This analysis can be extended to the chlorinated sucroses in Scheme C2(b), which are taken from the Table B3. The “usual” hydrogen bonds can no longer exist – except for that in structure **E** between the C2-OH and position 1′. Sugars **D**, **E**, and **H**, have axial chlorines at position 4. These should be very well accommodated in the hydrophobic domain. Would that feature help sweetness?

Notably, chlorinated sucroses **D**, **E** and **H** are highly sweet!

Appendix D: Sucralose Definitely Non-caloric; Carcinogenic? Very Unlikely

Can Sucralose (Splenda) Produce Energy: And Thereafter Fat?

In Sect. 5.2, the degradation of sucrose *versus* sucralose (the sweet ingredient in Splenda) was given a non-chemical presentation. A more rigorous depiction is now needed.

The disaccharide sucrose is readily cleaved into its monosaccharide components glucose (**2**) and fructose (**3**) by enzymes known collectively as sucrase. Intersaccharide cleavage can also be effected by mild acid hydrolysis {Scheme D1(a)}.

The glucose that is obtained by enzyme action is phosphorylated at position-6, as in compound **4**. The ring-opened, aldehydo form suffers deprotonation at C2 leading to ene-diol, **5**, which rearranges to give corresponding α-hydroxy ketone **6**. The latter is actually fructose 6-phosphate, which upon further processing leads to fructose-1,6-diphospate, **7**, a key biological intermediate.

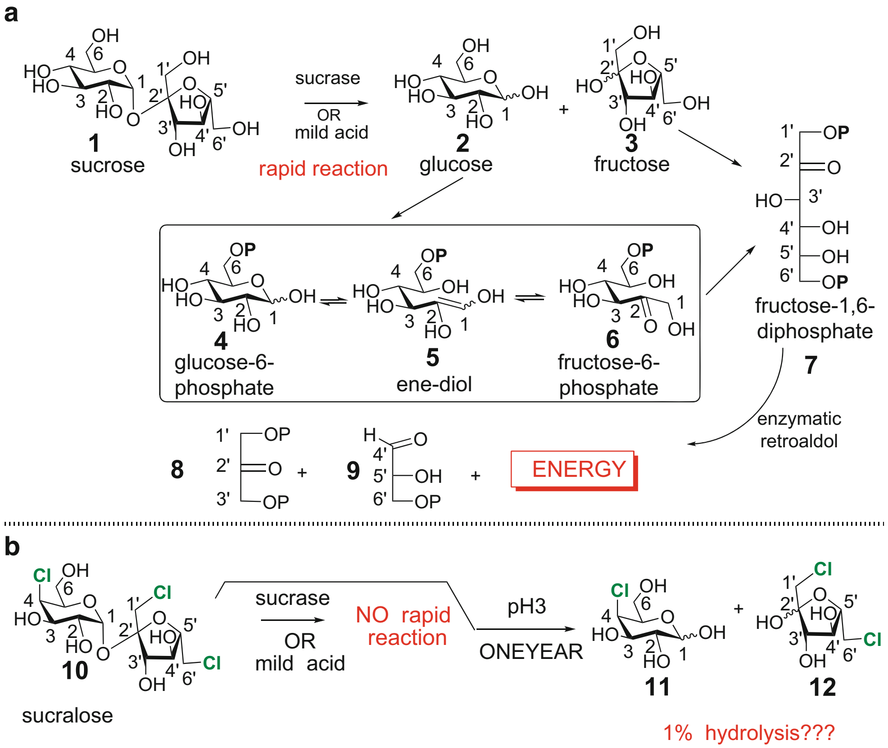
Cleavage into two 3-carbon fragments, which are structural isomers, dihydroxyacetone (**8**) and D-glyceraldehyde (**9**) is accompanied by copious liberation of energy. The 3-carbon fragments undergo further bio-processing, with the liberation of more energy.

The body uses this energy to perform vital functions such as sleeping, staying awake, thinking etc. Unused energy is stored hopefully for future needs, visibly as fat, and invisibly as glycogen.

Sucralose (**10**) is refractive to the enzyme(s) sucrase, and to mild acid hydrolysis, Scheme D1(b), and so bio-processing to give the 3-carbon fragments, with the attendant release of energy, does not occur.

The result is that sucralose can neither produce energy nor fat.

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3,



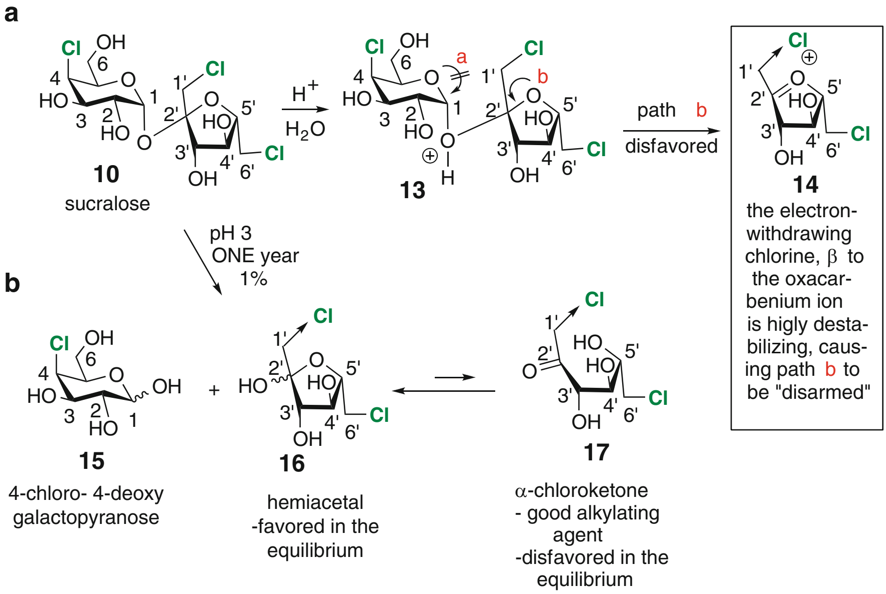
Scheme D1 Release of energy from sucrose *versus* sucralose

Accounting for the Differences Between Sucrose and Sucralose (Splenda)

It is interesting to speculate about the difference in acid hydrolysis of sucrose and its trichlorinated analog, sucralose.

The left-hand-side component of sucrose is a 6-membered (pyranoside) ring, while the right-hand-side is a 5-membered (furanoside) ring. Generally, 5-membered rings are more reactive than their 6-membered counterparts, and this holds true for sugar derivatives. Thus furanosides are hydrolyzed much more readily than pyranosides.

Cleavage of sucrose derivative can be assumed to begin with protonation of the intersaccharide oxygen. In the case of sucralose, **10**, such protonation would give **13,** Scheme D2(a). If cleavage were to occur, the left-hand or right-hand ring oxygen would have to be engaged as depicted by the arrows *a* and *b* in **13**. Given



Scheme D2 A possible route to acid hydrolysis of sucralose

the principles stated in the preceding paragraph, furanoside cleavage, should predominate, as depicted by pathway *b*, and this would lead to oxocarbenium ion **14**.

Formation of the latter **should** be facile since it is a tertiary carbocation, stablilized by resonance with the α-(ring) oxygen. However, the β-chlorine at position-1’ provides a strong deterrent. The effect of such an electron withdrawing group is to deplete electron density from the incipient carbocation, thereby disfavoring formation of **14**. Such electronic effects have been extensively studied in the author’s laboratory under the rubric of the “armed/disarmed” phenomenon [1].

The outcome of these conflicting electronic forces is that acid catalyzed solvolysis of sucralose is strongly disfavored. This was actually observed by Jones and coworkers in their 1958 publication dealing with the first attempts to chlorinate sucrose. Thus they reported that “the vigorous conditions of hydrolysis necessary to cleave the interglycosidic linkage **destroyed the fructose** moiety. . .” [2] (emphasis added).

In keeping with the above, it was reported that sucralose was not cleaved by dilute acid. On the other hand, when the compound was left at room temperature for one year at pH 4, (the acidity of vinegar), there was no detectable hydrolysis. However with a slightly stronger acid at pH 3, sucralose was hydrolyzed to the extent of 1% in 1 year [3].

Toxic and Carcinogenic? Not Very Likely

Hemiacetal **16** galvanizes attention. Equilibration gives the related ketose **17** which, being an α-chloroketone, would be an excellent alkylating agent. A woeful Cassandra can certainly conceive of a scenario where structure **17** runs rampant through the human body alkylating every piece of DNA that it encounters.

However such depredations are unlikely. (i) The extremely slow hydrolysis of **10** means that the concentration of **16** is going to be very, very small. This acetal (**16**) could equilibrate with the α-chloroketone **17**; (ii) but we know that α-halo carbonyl compounds are readily hydrated. Chloral hydrate is a classic example. For the same reason the equilibrium favors hemiacetal **16**. Items (i) and (ii) combine to ensure that the population of the potentially dangerous product **17** will be vanishingly small.

This theoretical conclusion is supported by the following quotations from a 2008 survey by Frank [4]. With regard to toxicity: "Results from over 100 animal and clinical studies included in the FDA approval process unanimously indicated a lack of risk associated with sucralose intake," With regard to carcinogenicity: "Sucralose administration resulted in no effect upon tumor frequency—in comparison with controls." With regard to teratogenicity (effect on fetal development): "The progress of pregnancy and fetal development in rats and mice were unaffected by sucralose levels exceeding maternally tolerant levels."

In Sect. 3.1.6 we discussed Jones' rationalization for developing a pesticide by replacing a few of the hydroxyls of sucrose with chlorine [2]. The resulting substance could be considered an organo-chloride, a description which immediately evokes the memory of an infamous organo-chloride, DDT. However there are huge differences between both. For one thing, DDT has no hydroxyl groups, and is therefore not water soluble, a property which makes bio-degradation virtually impossible. On the other hand it is soluble, and accumulates, in fatty tissue. Thus when DDT was used as a pesticide it ended up in rivers, in the fatty tissue of fish, where free-radical induced dechlorination has toxic effects [5].

By contrast, a partially chlorinated sugar would be water soluble, and hence biodegradable. Indeed, Labare et al. report that "sucralose is digestible by a number of microorganisms and is broken down once released into the environment." [6].

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Appendix E: Patents Old and New

Expired: But Still Important

Appendix B gave an overview of the syntheses of what-came-to-be-known as sucralose, by the labs of Hough and Khan. In January 1976, these groups jointly filed British patent No. 1,543,168, with Khan, Hough and Phadnis as inventors and RESEARCH CORPORATION of New York as Assignee, for the preparation of “Chloroderivatives of sucrose”. Also in January 1976, British patent No. 1,543,167 was filed with Tate and Lyle as Assignee, describing various sweet chlorinated sucrose derivatives. Kahn, Hough and Phadnis, of the first patent, were also named as inventors for the second, and the name of Jenner was added.

(For clarification of how the above patents came to be divided see comments by Professor Hough in Sect. 4.1.6).

Three other expired patents that had an impact on the trial are −869, -476, -746 and so they will be discussed below. The Vilsmeier Reaction [1, 2] was used in most of the patents, and so a brief discussion about its mechanism is given first.

A Note About the Vilsmeier Chorination Reaction

The Vilsmeier reaction was first applied for chlorination of sucrose in a paper by Khan and co-workers in 1975 [3]. Their choice of acid chloride for the reaction was methanesulfonyl chloride. The Vilsmeier procedure is, arguably, less vicious than the classic sulfuryl chloride method, employed by Helferich [4] and Jones [5]. This modern chlorination procedure was to become of major importance in the manufacture of sucralose, as was evident in the first patent to be filed in the USA by a Tate & Lyle subsidiary (No 4,380,476), by Inventors Khizar S. Mufti and Riaz A. Khan in 1981.

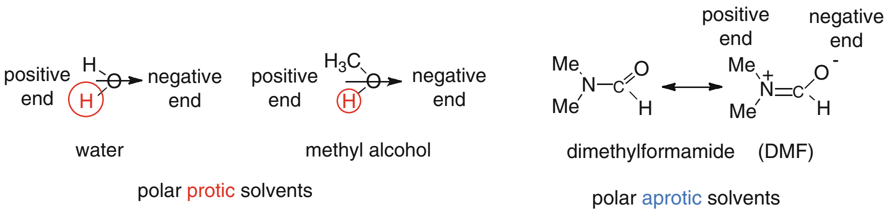
The patents use the term “polar aprotic” solvent. What does this mean?

B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3,

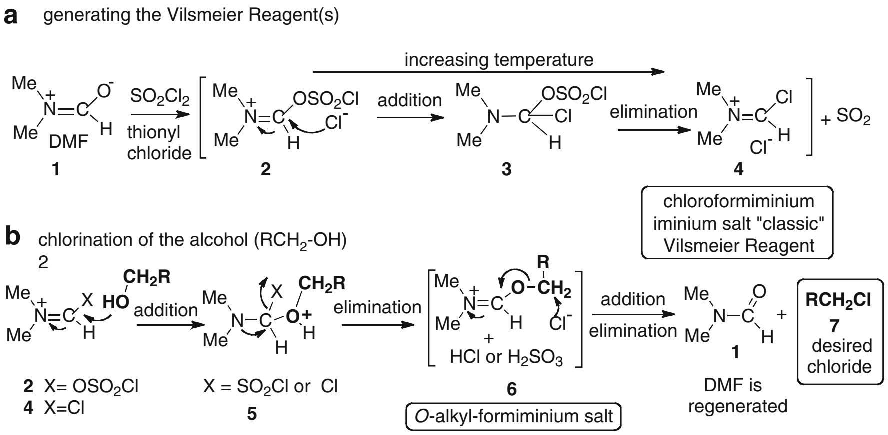
Solvents like water and methanol have + ve and –ve “ends” (as seen in Scheme E1)– although the overall molecule is neutral. This property makes them *polar* solvents, and enables them to dissolve substances like sugar and salt. The red hydrogen of each can depart as a proton through ionization. They are therefore **polar protic** solvents.

Dimethylformamide (DMF) is known to exist in dipolar form, with + ve and –ve domains (Scheme E1). Its nuclear magnetic resonance spectrum indicates that the two methyl groups are different. This is because the molecule spends most of its time as depicted on the right-hand-side where rotation about the double-bond is prohibited. The two methyl groups therefore never experience the same environment, for one is *cis* to oxygen, while the other is *cis* to hydrogen. However the molecule does not have an easily removed proton, therefore DMF is a **polar aprotic** solvent.

In Scheme 7.4, a simplified mechanism of the Vilsmeier chlorination reaction was given. A more elaborate version is now shown in Scheme E2(a). The acid chloride, which in this case thionyl chloride, acylates the electron-rich oxygen of dimethylformamide (DMF) to give **2** with liberation of a chloride ion. Structure **2** has been identified by several early workers, notably Kikugawa [6], and it



Scheme E1 Polar protic and aprotic solvents



Scheme E2 A possible mechanism of the Vilsmeier chlorination reaction (cf. Scheme 7.4) corresponds to the "low temperature structure **A** in Scheme 7.4). As the temperature increases [6], the liberated chloride ion makes a nucleophilic addition to the iminium ion to give a tetrahedral intermediate **3** from which sulfur dioxide is expelled leading to the chloroformiminium chloride salt **4** (cf. structure **B** Scheme 7.4). This can be isolated as a stable white solid and is commercially available as the Vilsmeier Reagent.

Structures **2** or **4** have nucleofugal vinylic substituents, chlorosulfate and chloride respectively. An alcohol, e.g. RCH_2OH, can make a nucleophilic attack on either, as shown in Scheme E2(b), to give the tetrahedral intermediate **5**, en route to the *O*-alkyl-formiminium salt **6** which can be very stable. However upon heating, attack by chloride on the alkyl residue is facilitated by the ease with which DMF is liberated, accompanied by the alkyl chloride **7**.

One of the most elegant aspects of the process is that DMF, which is used in the first step for reagent formation, is regenerated in the last step. This is very economical for an industrial manufacturing process.

The merit of DMF as a polar aprotic solvent, is that it can dissolve polar substances, like sucrose, as well as the non-polar, like the chlorinated sucroses, which are formed during the course of the reaction.

Patent 4,362,869

Inventors:	Michael R. Jenner, David Waite, Graham Jackson, John C. Williams
Filed:	December 4, 1980
Assignee:	Talres Development

This patent is one of two patents where the Assignee is Talres Development. The other is the 476 patent which follows.

The invention reports an improved procedure for migration of the acetyl group from position 4 to 6 as discussed in Appendix A. This improvement goes a long way towards enabling a better yield of sucrose pentaacetate triol **10.** The subsequent reaction, with sulfuryl chloride, also gives **11** in better yield.

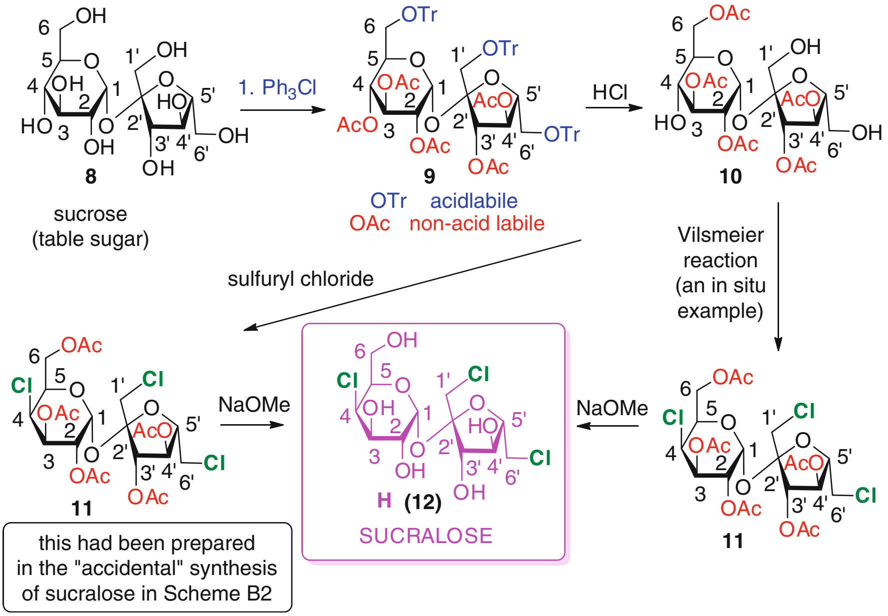
An alternative route to **11** is by reaction of the migration product **10** with the Vilsmeier reagent. Deacetylation of **11** with sodium methoxide then gives sucralose.

The caption for Example 7 of the 869 patent reads:

> "4,1',6'-Trichloro-4,1',6',-Trideoxygalactosucrose Pentaacetate Using a Vilsmeier Reagent Formed **in Situ".**

The words "in situ" are emphasized because, as will be seen, they played a major, decisive role in the trial. However, the words have been associated with the Mufti patent (476) that follows, as being the originators of the "in situ" Vilsmeier reaction in sucrose chemistry.

I wonder why?



this had been prepared in the "accidental" synthesis of sucralose in Scheme B2

Scheme E3 Summary of the 869 patent

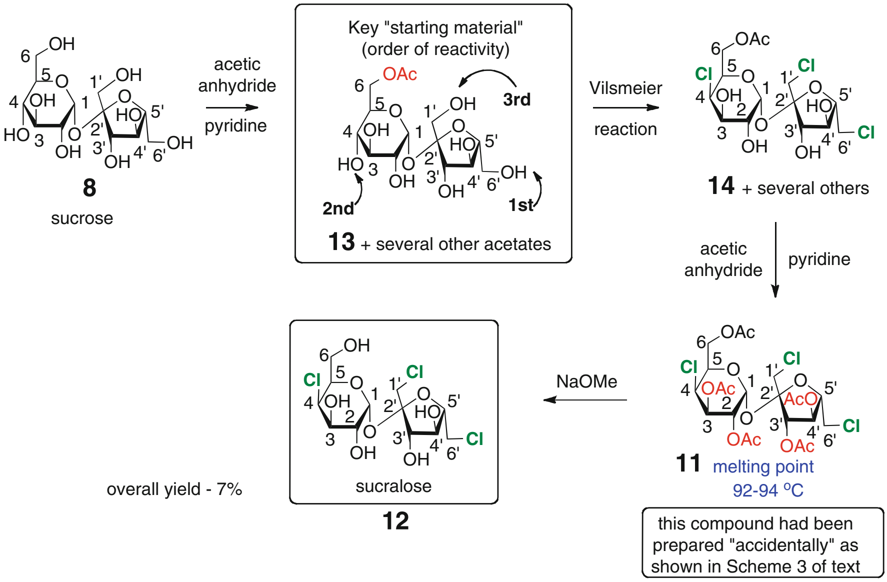
Patent 4,389,476 (The Mufti Sword of Damocles)

Inventors:	Khizar S. Mufti, Riaz A. Khan
Filed:	June 19,1981
Issued:	April 19, 1983
Assignee:	Talres Development

Patent No: 4,389,476 issued on April 1983 with Mufti and Khan as Inventors (Scheme E4) had a visceral effect on the trial. The Inventors had rejected the “round about” route for blocking position-6 that they had used 8 years earlier (Scheme B2, Appendix **B**). In view of the “most reactive” status enjoyed by position-6, the Inventors reasoned that direct acetylation at this site should be the predominant reaction. Indeed conditions were developed that gave compound **13** (Scheme E4) *mainly,* but alas with other acetylated products.

The isolation of **13** was of major importance, because earlier experiments in Hough’s lab had shown that if position-6 was “blocked” the EXPECTED order of chlorination of the remaining hydroxyl groups should be:

(i) Position-6’, then
(ii) Position-4’, then
(iii) Position-1’



Scheme E4 Summary of Mufti-Khan 476 patent

It was assumed, reasonably, that Vilsmeier chlorination of the mixture containing **8** would occur at the three desired positions indicated in **13**, to give **14** (mainly). The mixture from the Vilsmeier chlorination was therefore directly peracetylated, and the resultant mixture, upon skillful processing, yielded **11** as a crystalline compound.

Notably, the key crystalline compound **11** had been obtained by both Khan and Hough six years earlier – as Scheme B2. The material was therefore deacetylated to obtain the desired sucralose, **12**.

Unfortunately, the overall yield of sucralose by the route in Scheme E4 was only 7% – certainly not a good prospect for industrial scale-up purposes.

So why did the '476 patent become so crucial in the trial?

The Vilsmeier Reagent is "normally" prepared by doing step (a) of Scheme E2 first, and isolating the chloroforminium chloride salt **4.** This exists as stable white crystals that can be stored for days, and even purchased from chemical supply houses. The salt **4** is then used subsequently in step (b).

The patent (issued in 1983) reports that the reagent can be prepared as described above, but goes on to say:

> **"The reagents may also be formed *in situ*,** but are preferably prepared in advance and isolated before being used." (page 4 lines 20–22)

(I noted at the end of discussion about the 869 patent, that it included an example of an ***in situ*** process. That was *before* the 463, but for some reason this earlier example was not featured in the trial).

A legal wrangle consuming hours of time before and during the trial was focused on the words **"*in situ*".** This is because a claim of the allegedly infringed 463 patents (issued in 1990 – seven years later) states, that the Vilsmeier salt could be prepared "in the presence of the" compound to be chlorinated. The lawyers for the Respondents would assert that the underlined words had the same meaning as **"*in situ*",** and thus the newer 463 patent should not have been issued, since it was a repetition of the **Mufti** 476 patent. If it should not been issued, it cannot have been infringed!

A battle of the meaning of words **"*in situ*"** was therefore joined.

(It is appropriate to note here that in Sect. 7.8, I speculate that the strategy used by the Chinese manufacturers appeared to be an update of the **Mufti** patent).

Patent 4,950,746 (The 746 Patent)

Inventor:	Juan Navia
Filed:	July 18 1988
Issued:	August 21, 1990
Assignee:	Noramco, Inc. Atlanta, Ga

The crucial aspect of the 746 patent rested on one word, with three letters – "tin". The 746 patent which follows shows why "tin" was so important.

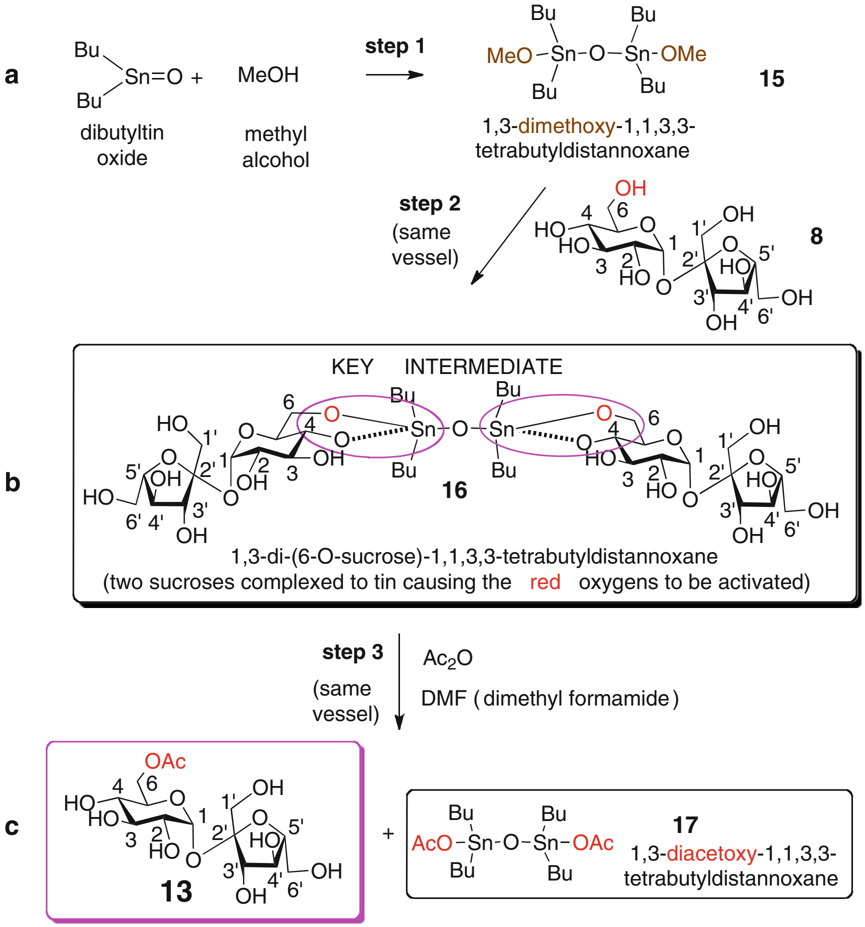
This 746 patent, invented by Juan Navia in 1988, shows that industrial production of sucralose had now moved to North America. Tate & Lyle held the patent on sucralose; but because the compound is 600 times sweeter than sucrose, it had to be "cut" so that it could be used conveniently as an artificial sweetener. Since they had no experience with that sort of formulation, Tate & Lyle formed a partnership with McNeil Specialty Chemicals, a subsidiary of the US giant Johnson and Johnson which developed the formulation now known as Splenda. The collaborators also "invented" the word *sucralose*, thereby dispensing with the clumsy technical name.

Interestingly FDA approval of Splenda was very slow in coming, undoubtedly reflecting the pressures of the then prominent sweeteners. Approval in Canada was given nearly 10 years earlier in 1991.

The strategic "blocking" of position-6 to obtain **13** had been partially successful as indicated in Scheme E4. Nevertheless, the procedure developed by Mufti and Khan, though ingenious and heroic, involved such a rich mixture from the very start. that at-the-end-of-the-day, sucralose was isolated in only 7% yield.

A better strategy for "blocking" position-6 *selectively,* without affecting the other primary hydroxyls of sucrose was therefore needed, and in order to understand how this was done, we must take a more sophisticated look at the shape of sucrose.

As noted in Appendix C, an alternative to the Haworth projection (with OH groups going "up or down" as in Scheme E4), is the "chair-like" profile or



Scheme E5 Navia's elegant "tin" synthesis of starting material **13**

conformation. In this profile the OH (hydroxyl) groups at positions-4 and 6 of the glucose segment are seen to be very close. (Contrast the representations of sucrose **8** as depicted in Schemes E4 and E5).

Indeed, the OH groups at positions-4 and 6 are close enough to be bridged. In this regard, the metal tin, for which the symbol is Sn, (its Latin name is *stannum*) has derivatives that like to form bridges between two OH (hydroxyl) groups [7].

Since there are eight hydroxyl groups, one might think that there are several possibilities for bridges to form; but the tin derivative is very partial to 6-membered bridges. The hydroxyls at position 4 and 6 are ideal for such a tin bridge. It is seen in Scheme E5 that **two** sucrose molecules can be brought together back-to-back and held there by complexation to one tin derivative. These complexes are encircled in structure **16.** (Readers who are familiar with tin chemistry may consider the *bis* complex unusual; but Navia obtained compound **16** as a crystalline substance, and established the structure by elemental analysis).

Can another 6-membered bridge be formed between positions-4' and-6' of the five-membered (fructose) moiety?

No, not very readily, because such a bridge would contort the five-membered ring unacceptably.

Notably all other pairs of hydroxyl groups can only form five-membered rings and so do not compete.

A further advantage of complex **16**, is that tin enhances the reactivity of the oxygen to which it is attached [6]. Thus the complexation gives position-6, which is already favored, a substantial boost in its reactivity, with the result that product **13** is obtained with exquisite purity, rather than in a mixture as in Scheme E4

With an efficient route to the key intermediate, **13**, the task was now to employ the Vilsmeier chlorination protocol efficiently. This was addressed in the 463 patent.

The Alledgely Infringed 463 Patent. Patent 4,980,463 (The 463)

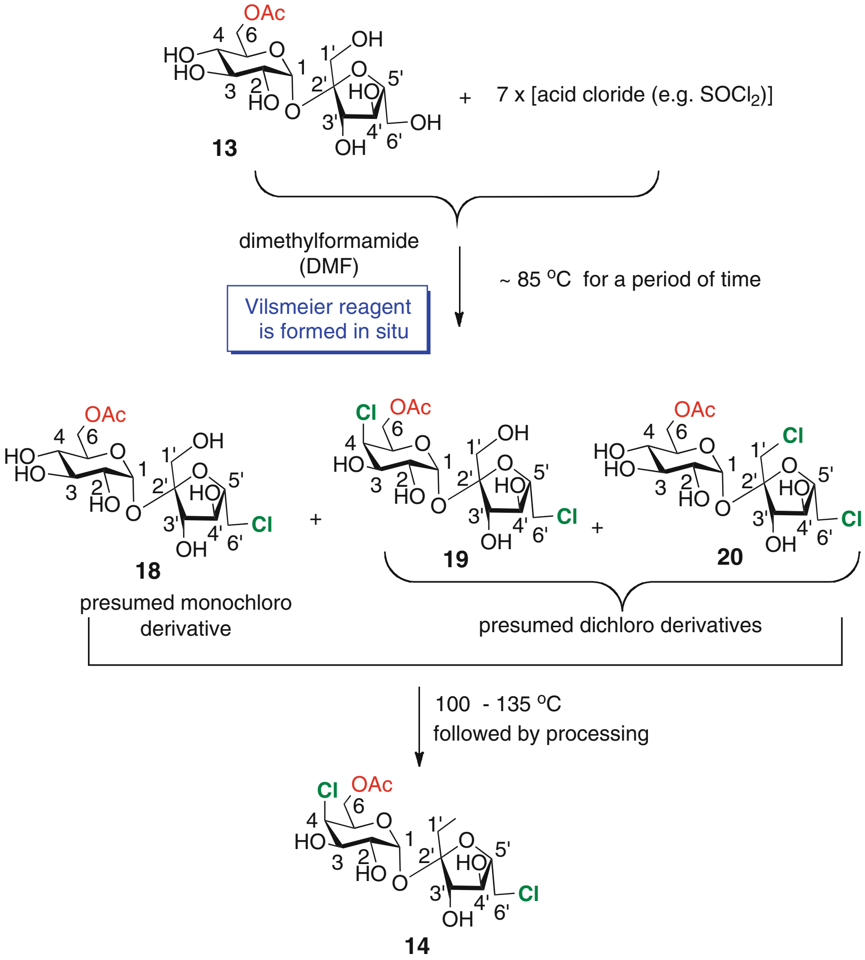
Inventors:	Robert E. Walkup, Juan L. Navia, Nicholas M. Vernon
Filed:	July 18, 1989
Issued:	December 25, 1990
Assignee:	Noramco, Inc. Atlanta, Georgia.

Navia's procedure to obtain the acetate **13** with excellent selectively was a major development of the 746 patent, and the task now, was to leverage its advantages. The efficiency of the process would be compromised unless the subsequent chlorination leading to sucralose, was equally efficient.

This was the challenge faced by the 463 patent filed a year later (July 18, 1989). Navia's choice of dimethylformamide (DMF) for the acetylation of his tin complex **16**→**13** (Scheme E5), had an additional advantage for the upcoming chlorination reaction. We have commented (Scheme E2) on the elegance of the Navia process in Scheme E5, since DMF serves as the solvent for the entire conversion of sucrose to sucralose, as well as functioning as an ingredient for the Vilsmeier reaction.

But some obstacles lay in the way. Chlorinations of **13** at the three desired positions would have to be properly executed, or an awful mess would result. And this would not be easy because these are vigorous reactions – first in *formation* of the Vilsmeier reagent, and second in its *use*. These reactions are accompanied with evolution of copious heat which means that reaction could "take off" i.e. go entirely out of control. But less theatrically, the copious heat could provide enough energy to induce chlorination of the more stuborn sites, particularly the 1' position.

Thus, the temperature inside the reaction vessel had to be rigorously controlled during the entire chlorination process. Even so, in chemistry what one expects is not



Scheme E6 Summary of the 463 patent

necessarily what one gets. Thus the above noted order of reactivity for the three positions of interest, positions-6’, then 4, then 1’ is fine for theory, but maybe Nature has different ideas (Scheme E6).

The validity of a patent rests on the claims which it makes. These are usually found in the last pages of the document. They may be summarized as follows:

1. The previously prepared acetate **16** is dissolved in DMF.
2. “At **least 7 molar equivalents** of - - - - an acid chloride (e.g. $SOCl_2$)$^{\#}$ - - - are added - - - - - “whereby the chloroformiminium chloride salt - - - [i.e. the classical Vilsmier reagent] - - - forms an O-alkylformiminim chloride adduct with the hydroxyl groups of the sucrose-6-ester (**16**). $^{\#}$ *many other “acid chlorides” are exemplified.*

3. The reaction mixture is heated "to an elevated temperature not higher than about 85° C for a period of time sufficient to produce a mixture of chlorinated sucrose-6-ester products consisting essentially of monochlorosucrose-6-ester*," **18** and dichlorides **19** and **20**$^{\#}$. (These correspond to **products #1, #2** and **#3** in Scheme 7.3). **The Brief Summary of the Invention at the beginning of the patent states that the dichloro esters* [are] "believed to comprise primarily" **19** and **20**.
4. The reaction mixture from step 3 - - - is subjected "to an elevated temperature of at least about 100°C but not higher than about 130°C for a period of time sufficient to produce a chlorinated product comprising predominantly the trichloro-monoacetate **14** .
5. The product from step 4 "is recovered by extraction with a solvent that works well with the trichloro compound **[14]** - - - but does not work well with di-chloro- and mono-chloro-sucrose-6-esters."
6. "The process - - - includes the step of neutralizing the reaction mixture - - - with aqueous alkali **to regenerate the hydroxyl groups at positions 2,3,3' and 4'** of the trichlorinated sucrose-6-ester.

There are MANY questions which can be, and indeed were, asked about these claims. These were raised in court, and are discussed in the main text.

Patent 5,034,551 (The 551 Patent)

Inventors:	Nicholas M. Vernon, Robert E. Walkup
Filed:	April 23, 1990
Issued:	July 23, 1991
Assignee:	Noramco, Inc. Athens, Ga.

The 551 patent is concerned with recycling the tin catalyst that was used so efficiently by Navia in his 746 patent. From Scheme E5, it is seen that in step (a), dibutyltin oxide reacts with methyl alcohol to give structure **15.** This is Navia's preferred catalyst to react with sucrose giving key intermediate **16.** The next step involves acetylation to give the desired material **13.**

Thus, during the operation of the 746 patent, the preferred tin promoter, **15**, undergoes a transformation in which the MeO (methoxy) groups are replaced by AcO (acetate or acetoxy) groups giving **17**. The latter is therefore a "by-product" of the reaction.

But there are at least two reasons why this by-product should not be discarded. First, it would be uneconomical to do so. Second, tin compounds are toxic to humans and are also environmentally unfriendly. They therefore cannot be simply "discarded."

Isolating the "by-product", **17**, and converting it back to the preferred catalyst, **15**, needed for the first step, was therefore a desirable, economical, and attractive undertaking. The difficulty was that at the end of the reaction in Scheme E5, the desired material, **13**, and by-product, **17**, are accompanied by other impurities that complicate efforts at isolation. The root cause is that DMF, being a polar aprotic solvent, dissolves, or is soluble, in just about any other solvent. Thus if water is poured into the reaction vessel, it will mix with the DMF. On the other hand if an organic solvent is poured in, it too will mix with the DMF.

But with seven free OH (hydroxyl) groups, compound **13** should be (more) soluble in water than (many) organic solvents

The trick, which probably required countless trial-and-error experiments, was to add only a small amount water, and to find an organic solvent which, when added to the resulting mixture, would cause two layers to form. Ideally, the upper layer should be DMF + water + **13**, and the lower layer should be the organic solvent + the tin derivative.

The claims of the 551 Patent were therefore:

1. For a process to treat the reaction mixture with “a small amount of water–[and]—and an organic solvent# that is substantially immiscible with water to form—an extraction mixture, wherein the amount of water employed is sufficient to cause efficient partitioning……” of the solution inside the vessel into a “first phase” and a “second phase”. #Examples of suitable organic solvents include “chlorinated hydrocarbons”, heptane, cyclohexane and methyl t-butyl ether.
2. “[A]gitating the extraction mixture—[for a time and at a temperature] — to obtain a two-phase mixture - - - - - - ” with the tin by-product **17** “contained in said second phase - - - - ” (i.e. lower organic phase), and “essentially all of - - - [**13**] - - - - - - - contained in said first phase - - - - - ” (i.e. DMF + water layer).
3. The isolated tin by-product, **17**, “is subjected to - - - reaction with methanolic alkali to produce thereby - - - - ” **15.**

In typical patent format, there is much broadening and padding to encompass all conceivable analogs of **15** and **17**, as well as polar aprotic solvents other than DMF.

Patent 5,470,969 (The 969 Patent)

Inventors:	George H. Sankey, Nicholas M. Vernon, Robert E. Wingard, Jr.
Filed:	May 2, 1994
Issued:	November 23, 1995
Assignee:	Noramco, Inc. Athens, Ga.

The 969 patent goes one step further than the 551 patent in enhancing the efficiency and economy of Navia’s procedure disclosed in the 746 patent. Thus the 969 patent effectively avoids having to regenerate the tin promoter **15** from by-product **17**. The 969 patent shows that the diacetoxy tin-byproduct **17** generated as a by-product in the Navia process (see Scheme E5) can actually be used as the promoter for installing the acetate at position 6 of sucrose (see Scheme E5). So after the formation of **13** is completed, the by-product **17** just has to be isolated, purified and recycled. Thus, the 969 patent, discloses that the "spent" organic tin can actually be used in the synthetic procedure with great success.

The challenge here is that the organic tin and the various compounds from which it is to be separated are all liquids. Separating one liquid from another is actually a fairly common task in chemical operations, but the patent was granted in this particular case.

This series of three patents 746, 551 and 969 disclose some very elegant chemistry. I have chosen to describe the 6-acetate **13** as the "starting material" even though so much effort, skill and time goes into its preparation at the outset. This description of **13** as the "starting material" is justified because, only after there had been reliable access to it, could the potentially problematic chlorination steps be addressed.

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About the Author

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Fraser-Reid is previous winner of the Claude S. Hudson award of the American Chemical Society, the Alexander von Humboldt Senior Scientist Award from Germany, and the Haworth Medal of the Royal Chemical Society.

Fraser-Reid, who is a native of Jamaica, received his tertiary education in Canada and England. He is an accomplished musician on the piano and organ, having given recitals at chemistry conferences in Stockholm (Sweden), Seville (Spain), Sydney, Kingston (Jamaica).

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B. Fraser-Reid, *From Sugar to Splenda*,
DOI 10.1007/978-3-642-22781-3,

Epilogue

As I Stepped Down From the Witness Box

At the end of the redirect examination by "my" lawyer, Mr. Gary Hnath on Day 8 of the trial (Chap. 17), I was somewhat confused. I had expected to be pummeled by re-cross examination questions from the Complainant's lawyers, and so I continued to sit in the witness box expectantly, nervous and fearful. The para-legal assistant, who had guided me through the protocols for last 6 h, leaned over with some concern, and whispered to me "You may step down."

I obeyed him. I was conscious that the atmosphere in the Court room was, to put it mildly, mixed. Para-legals rushed to take photographs of the sketches that I had made on the make-shift blackboard during my impromptu tutorial. These sketches had been used to supplement and clarify the formally submitted documents that Judge Bullock had described as "Dr. Fraser-Reid's Demonstratives".

The commotion in the room was penetrated by thunderous outcry that my testimony was unacceptable and should be stricken because, coming near the end of the trial as it did, it could not be subjected to proper cross examination and evaluation. Indeed such evaluation would have been impossible anyway, because I was the only chemistry expert who was present in the room. The others, for both sides of the litigation, had already left town.

As I made my way to the back of the room, past the lawyers' preserve, a crowd of Chinese people approached me. They made no attempt to stifle their emotions. I assumed that they were affiliates of the four manufacturers who had been accused of infringing Tate & Lyle's patent for preparing sucralose, plus the many others who had trafficked in Chinese made sucralose.

At the front of the crowd were representatives of my employer, Guangdong Food Industry Institute. "You even brought up DNA!" exclaimed Dr. Wang, the Institute's Director, who was clearly puzzled by how this ubiquitous genetic molecule could find its way into this patent infringement lawsuit dealing with artificial sweeteners. His colleague, Ms. Hellen Churong Li, complimented me on being a "Real expert".

B. Fraser-Reid, *From Sugar to Splenda*,
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I was naturally pleased; but there was need for caution. A judge who prohibits the chewing of gum in his court, would probably be appalled at the spontaneous outpouring that was taking place in his presence. And even though I was not so paranoid as to imagine that his ruling would be affected by this exhibition, why take a chance? I therefore urged them to cool it.

In truth, I did not flatter myself. I undoubtedly had helped to draw attention to an aspect of chemistry that was there for all to see on the first page of the 463 patent. Indeed, I *could* not flatter myself. I was humbled by the realization that in spite of countless readings, the crucial sentence "[t]he chlorination of partially protected carbohydrates is especially difficult, because side reactions, such as oxidation and elimination have a great tendency to occur" had not registered previously. How strange that it was on the night before (Chap. 16), when for want of 'something to do' I decided to read the 463 patent one more time.

The Aftermath

The spring of 2008 dragged into summer, and summer into fall as we waited to know whether our clients were "guilty as charged". I recalled in the Introduction, that it was September 22nd, thanks to the magic of e-mail, that I learned that Judge Bullock had ruled *against* the charge of patent infringement. But inveterate worriers will always find something to worry about. First, Judge Bullock's ruling would be reviewed, and a final decision would be issued four months later. This gave me no comfort whatever, for certainly the giant Tate & Lyle would not take this lying down.

Nor did the press. They immediately trumpeted the ruling's vast international and commercial significance. The September 23, 2008 issue of *The Financial Times of London* carried an article under the byline of Maggie Urry that was captioned "Tate & Lyle Hit by sucralose patent ruling". The second paragraph of the article stated that "Tate had accused three *(sic)* Chinese companies of infringing some of its patents for sucralose, which sells under the Splenda brand name - - - - also accused were 18 distributors that had imported and sold the rival product in the US".

Ms. Urry continued: "Sucralose contributed to volatility in Tate's share price as *hopes that it would make substantial profits from its virtual worldwide monopoly of a product in great demand (emphasis added)* have been countered by fears that generic competition would emerge to undercut prices".

The caption of an article in *The International Herald Tribune* of the same date was equally bleak. "Tate & Lyle loses patent infringement claim" was accompanied by a picture of blue and white bags prominently labeled "Tate Lyle" (the ampersand was not visible) moving down a conveyor belt. Small print beneath the picture stated that 'Tate & Lyle shares slid 11.2 percent because of the commission's decision'.

"Some analysts were downbeat" the *Tribune* moaned:

"We believe this case just illustrates the risks involved with Tate's portfolio" analysts at Numis said in a research note - - - - - the commission's ruling could lead to overcapacity in the sucralose market as new entrants join, and so have an impact on Tate & Lyle's profit margins."

But as expected, "Tate & Lyle, based in London, said Tuesday that it intended to appeal the preliminary ruling by a judge at the US International Trade Commission."

The on-line version of the *Wall Street Journal* reported the news one day later, September 24, 2008, under the caption "Ruling in Splenda Case May Hit Tate & Lyle's Margin." For emphasis, there was a picture showing a yellow packet of SPLENDA being emptied. "The news sent Tate & Lyle's shares to a four-year low—the stock has halved in price in the past two years."

Judge Bullock's September ruling, was upheld in a ruling by a six-member panel in January 2009.

"The company has long said that while a chemistry undergraduate could make small amounts of the product, its patented manufacturing process was the only viable way of producing it in commercial quantities." And so "Tate & Lyle said it will appeal the preliminary ruling - - - - "

However, Tate & Lyle apparently decided not to appeal the panel ruling, and also not to pursue the civil case that had caused attorney Ed Pardon to contact me on April 30, 2007 (see Preface).

One Year Later

Woeful Cassandras must necessarily prophesy doom. But as New York's Wall Street has shown, some companies are "too big to fail".

The Observer of Sunday 23 May 2010, carried a worrisome headline: "Tate & Lyle considers cutting out sugar as it refines core business".

Javed Ahmed joined Tate & Lyle as chief executive one year after Judge Bullock's ruling, and six months later he unveiled "a radical restructuring—which could even see the company quit its historic sugar business."

"—analysts believe that Ahmed has the opportunity to break with tradition and drop the sugar operation to concentrate on *higher margin business,* particularly in the US".

And just what could this *higher margin business* be?

Three Years Later

"Tate and Lyle is planning to reopen a US sucralose factory to meet demand, and could be on the lookout for acquisitions after strong full year results" begins the May 27th 2011 issue of MARKETFORCESLIVE blog of the *Guardian.* The headline was "Tate & Lyle to reopen US factory as profits rise".

Rachel Cooper wrote in the June 5, 2011 issue of *The Telegraph* "After Tate last week posted a £250 m annual profit, compared to a £116 m loss last time round, and announced plans to reopen a mothballed Splenda plant as demand for sweeteners picks up. Deutsche analysts were remaining bullish on the mid-cap stock."

Chinese Meet Tate & Lyle Again: This Time in Jamaica

And Jamaica has not been forgotten in this rebirth. Chinese industrialists have been in negotiation with the government of Jamaica to take over a huge segment of Jamaica's flagging sugar production, including Frome and Monymusk Estates that were once owned by Tate & Lyle.

The author was therefore interested in article on page 6 of Jamaica's *Weekly Gleaner* (May 26–June 1, 2011) headlined "Tate and Lyle hunting new five-year sugar supply deal". Paul Worthington, regional technical director for Tate and Lyle said: "We—have spoken to all players in the industry, including the local private owners and the Chinese————————"

Having dropped sugar to pursue "*higher margin business*", it can be assumed that the Jamaican sugar may no longer simply be "the perfect companion to tea". It is more likely needed as the raw material for making sucralose (Splenda). But the four Chinese Respondents who won the litigation can be expected to expand their production of sucralose, and so will need increasing amounts of sugar. So the Chinese respondents and Tate & Lyle complainants will need the same raw material!

And so 200 years later, Chinese are once again involved in Jamaican sugar production; but this time not as indentured labourers (Chap. 1).

Like the financial houses on Wall Street, Tate & Lyle appears too big to fail.

Will the same be true for Jamaican sugar now that it begets Splenda?

Jamaica should be so lucky!