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# Hugo (Ugo) Schiff, Schiff Bases, and a Century of β-Lactam Synthesis\*\*

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[2+2] cycloaddition  $\cdot$   $\beta$ -lactams  $\cdot$  history of chemistry  $\cdot$  ketenes  $\cdot$  Schiff bases

Dedicated to Professor George A. Olah on the occasion of his 80th birthday

## Hugo Schiff: From Germany to Italy

Schiff bases (imines) constitute one of the most widely used families of organic compounds,[1] not only as synthetic intermediates but also in coordination chemistry, [1f,g] and their chemistry is essential material in organic textbooks. The Schiff test is also often used, but who was Schiff? Many of the pioneers of organic chemistry in the 19th century are familiar figures, but the discoverer of these compounds is now almost forgotten, at least outside of his home department at the University of Florence in Italy, which bears his name. Hugo Schiff (1834-1915), born in the vibrant Jewish community in Frankfurt/ Main, Germany, was a prominent chemist a century ago, and his death was widely reported. [2] He studied in Göttingen and completed his dissertation "Über einige Naphtyl- und Phenyl-derivate" in 1857 with Friedrich Wöhler, famous for the synthesis of urea. His

dissertation included studies of the chemistry of aniline,[3a] experience he was to make good use of in his studies of Schiff bases. However, in the aftermath of the 1848-1849 revolutions these were tumultuous times in Europe. Schiff was actively involved in the events of the day, reportedly having met and corresponded with Karl Marx (1818-1883) and Friedrich Engels (1820–1895). [2e] Marx published the Communist Manifesto in 1848 and moved to London from Germany in 1849, while his followers were persecuted and sometimes even jailed. Because of his "rather advanced political views" [2c] Schiff found it expedient to emigrate to Switzerland in 1857 and was Privatdozent at the University of Bern. He moved to Italy in 1863, where his brother, Moritz Schiff (1823-1892), was a prominent physiologist in Florence, having been denied a position in Hannover owing to his service as a physician in the revolution of 1848 in Baden.

Thereafter Schiff spent his long career in Italy and continued teaching until 1915, the year of his death (Figure 1). Despite his "rugged and forbidding exterior" he was one who "continued to cherish the most gentle ideals" (Figure 2).<sup>[2b]</sup>

#### Schiff Bases

In Italy Schiff first obtained a position in Pisa, where in 1864 he studied the reaction of aniline with aldehydes, including acetaldehyde, valeraldehyde, benzaldehyde, and cinnamaldehyde, and he discovered that imines were formed (Figure 3). The first brief paper was entitled "A New Series of Organic Bases" ("Eine neue Reihe organischer Basen"), [3b] and Schiff reviewed the

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Figure 1. Hugo Schiff, lecturing, April 24, 1915.



Figure 2. Caricature of Hugo Schiff, who was loved and feared by his students. Courtesy of the University of Florence.

$$\begin{split} &2\,\text{N} \begin{cases} &G_{6}\text{H}_{5}\\ &\text{H}\\ &\text{H} \end{cases} \; + \;\; G_{x}\text{H}_{y}\Theta \; = \; N_{2} \\ &2\,\text{O}_{6}^{2}\text{H}_{5} \; + \;\; \text{H}_{2}\Theta\\ &2\,\text{N} \\ &\text{H} \end{cases} \; + \; 2\,G_{x}\text{H}_{y}\Theta \; = \; N_{2} \\ &\frac{G_{x}\text{H}_{y}^{\prime\prime\prime}}{G_{x}\text{H}_{y}^{\prime\prime\prime}} + \; 2\,\text{H}_{2}\Theta. \end{split}$$

**Figure 3.** Representation of the reaction of aniline with carbonyl compounds.  $^{[3a]}$ 

subject in 1867.<sup>[3c]</sup> In 1866 he also devised the Schiff fuchsin aldehyde test, <sup>[3d]</sup> which is still in use. <sup>[3e]</sup> His designation of these compounds as bases has persisted, although they are not used as bases in the conventional sense. Already in 1866 his imine synthesis was given a substantial discussion in August Kekulé's textbook *Lehrbuch der Organischen Chemie*, <sup>[3f]</sup> which repeated the classification of these compounds as bases, helping to ensure this as a lasting legacy of Schiff.

## Atomic Weights and the Karlsruhe Conference, 1860

Schiff depicted the formation of imines in a form not completely in accord with modern practice (Figure 3) but which implies the formulae shown in Equations (1)–(3). The barred symbols

$$2 C_6 H_5 N H_2 + C_X H_Y O = C_6 H_5 N C_X H_Y + C_6 H_5 N H_2 + H_2 O$$
 (1)

$$2 C_6 H_5 N H_2 + 2 C_X H_Y O = 2$$

$$C_6 H_5 N C_X H_Y + 2 H_2 O$$
(2)

$$\begin{aligned} & PhNH_2 + PhCH = O \\ & \rightarrow PhCH = NPh + H_2O \end{aligned} \tag{3}$$

 $\mathbb{C}$  and  $\mathbb{Q}$  denote the atomic weights  $\mathbb{C}$  = 12 and O = 16, which doubled the values previously in use, and reflected Schiff's good fortune in 1860 to attend the Chemical Congress at the Technische Hochschule in Karlsruhe, Germany, as a participant from Switzerland.[4] This first international scientific congress, hosted by Karl Weltzien, Professor at Karlsruhe, was called to discuss the problem of the atomic weights of the elements. There were 127 persons recorded in attendance, including many of the greatest names in chemistry, among them Dmitri Mendeleev, Friedrich August Kekulé, Carl Fresenius, Stanislao Cannizzaro, Charles Adolphe Wurtz, Julius Lothar Meyer, Robert Wilhelm Bunsen, and Alexander Borodin. None were present (or apparently invited) from the Americas or the Far East, reflecting their isolation from the main centers of chemical research. The meeting originated with Kekulé, who in 1858 proposed the tetravalence of methane, the existence of carbon chains, and the atomic weights C = 12 and O = 16. Kekulé suggested to Wurtz a meeting to discuss the problem of the atomic weights of the elements, said to have reached a state of anarchy, [4e] and met with Wurtz and Weltzien in Paris in March, 1860, to plan the event, which took place September 3-5, 1860. At the conference there was heated discussion and much strong disagreement, and on September 5 Cannizzaro (Figure 4), who had been a student in Pisa before discovering the reaction that bears his name, [5a] made a momentous address arguing for the acceptance of Avogadro's hypothesis, which required that the simple gases nitrogen and oxygen were diatomic, and required a valence for oxygen of two and four for carbon.

There was still disagreement, but at the close of the conference the delegates were given copies of a pamphlet written by Cannizzaro in 1858, *Sunto di un corso filosofia chimica*. <sup>[5b]</sup> Julius Lothar Meyer read this on his journey back to Breslau (now Wroclaw), and commented, "*I too got a copy which I put in my pocket to* 

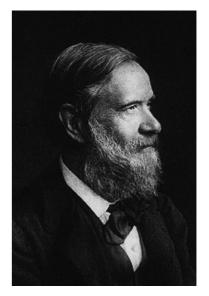


Figure 4. Stanislao Cannizzaro (1826–1910). Courtesy of The Edgar Fahs Smith Collection, University of Pennsylvania.

read on my home journey. I read it again and again and also at home and was astonished at the light which the writing threw on the most important points of issue. The scales fell from my eyes, doubts vanished, and a sense of the calmest certainty took its place."[2c][\*] Mendeleev (1834-1907), who, like Schiff, was only 26 years old at the time, was also powerfully impressed, later recalling "I vividly remember the impression produced by his speeches, which admitted of no compromise, and seemed to advocate truth itself...the ideas of Cannizzaro proved, after a few years, to be the only ones that could stand criticism."[4j] Both he and Lothar Mever wrote influential textbooks which supported the theory and included the first modern periodic tables. This led to a rapid growth in chemical understanding, which soon reached a state recognizable today.

It was noted that after the first session "the members fraternised together at a banquet laid for 120 persons in the large hall of the Museum. This supplementary meeting, which was not

<sup>[\*] &</sup>quot;Auch ich erhielt ein Exemplar, das ich einsteckte, um es unterwegs auf der Heimreise zu lesen. Ich las es wiederholt auch zu Hause und war erstaunt über die Klarheit, die das Schriftchen über die wichtigsten Streitpunkte verbreitete. Es viel mir wie Schuppen von den Augen, die Zweifel schwanden, und das Gefühl ruhigster Sicherheit trat an ihre Stelle." [4]

mentioned in the programme, was by no means the least scientific, the least relished, nor, above all, the least substantial." [4h] This set a convivial tone for future meetings, a tradition which has continued.

Thus Schiff at the beginning of his career had intimate contact with many of the world's leading chemists, and years later was, along with William Odling (1829–1921, who had been Professor at Oxford, President of the Chemical Society of London, and creator in 1864 of an early periodic chart), one of the last surviving participants at this epochal event.

#### Schiff in Florence

By his 30th birthday in 1864 Schiff was a well-established scientist with more than 50 papers to his credit. He also engaged in a vociferous debate with A. W. Hofmann in London on the formation and constitution of the aniline dyes, and this spurred Hofmann to important discoveries regarding the phenylamines.<sup>[6]</sup>

After a brief stay in Pisa (1863–1864) Schiff moved to Florence to teach chemistry in the Museo di Storia Naturale (1864–1876) and was a co-founder of the journal *Gazzetta Chimica Italiana* in 1870 along with Cannizzaro and other prominent Italian chemists (Figure 5). This journal was prominent for more

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Sko i to bettembre 1870.

mentre suonarono le campane per la

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fu fondato

In questo Laboratorio di Chimica

(Via Romana 18)

La Gazzetta Chimica Italiana

presenti i Prof. Stan Cannizzaro

Branc Irlmi

Roto Cafrinari

Ugo Sohiff

Luigi gabba

e gli aiuti: Incaretto.

Figure 5. Founding document, Gazzetta Chimica Italiana, 1870. Courtesy of the University of Florence.

than 120 years before becoming part of the combined European journals, the European Journal of Organic Chemistry and the European Journal of Inorganic Chemistry. In 1877 he became Professor of General Chemistry in Turin but returned to Florence in 1879 as Professor of General Chemistry in the Istituto di Studi Superiori Pratici e di Perfezionamento (after 1924 the University of Florence).[2b] Schiff continued to be a very prolific investigator, and his publication list over a period of more than 60 years grew beyond 300 papers in organic, inorganic, physical, biological, and applied chemistry. These were in German, Italian, or French, and in a few cases the same paper appeared in two different languages, which was an accepted practice at the time.

Schiff retained his liberal views and was a cofounder of the socialist Italian newspaper L'Avanti in 1894, which is still in existence. Cannizzaro, who shared this outlook, was characterized as having the fiery temperament of his native Sicily, leading him to fight in the rebellion against the King of Naples in 1847-1849 and to join in 1860 with Garibaldi in Palermo. Mendeleev had a similar progressive attitude and resigned his Professorship at the University of St. Petersburg in 1893 when rebuked for his sympathy with student unrest, and he was never admitted to the Imperial Russian Academy of Sciences.

## 100 Years of $\beta$ -Lactams by [2+2] Cycloaddition

A new and far-reaching application of imines came soon after the preparation and isolation of diphenylketene (2), the first ketene, in 1905. [7a] Hermann Staudinger (Figure 6) found in 1907 that 2 reacted with Schiff bases such as 1 by [2+2] cycloaddition, [7b] producing the first synthetic  $\beta$ -lactam 3 [Eq. (4)]. In the same report were included the corresponding preparations of  $\beta$ -lactones and of cyclobutanones, and this



Figure 6. Hermann Staudinger (1881–1965). Courtesy of the ETH Zürich.

began the study of cycloadditions, 20 years before the discovery of the Diels-Alder reaction.

The reaction of imines with ketenes forming β-lactams was discovered 100 years ago, long before the utility of the products in medicinal chemistry was recognized. For this reason the reaction remained a little-used laboratory curiosity until the discovery of the potent antibiotic penicillin.[8] When the therapeutic properties of penicillin were recognized there was a massive effort to prepare large quantities of this wonder drug and to deduce the structure with the hope of developing a laboratory synthesis. [8,9] A critical step in the proof of the β-lactam structure for penicillin was the realization by R. B. Woodward that normal amide conjugation was hindered in the strained nonplanar bridgehead bicyclic β-lactam structure, so that the β-lactam was more reactive than normal open-chain amides, and the normal amide IR absorption  $1670 \text{ cm}^{-1}$ was displaced 1728 cm<sup>-1</sup>.[8c] The first synthetic penicillin 7 (classified as a penam) was prepared by [2+2] cycloaddition of imine 5 with ketene 4 in 1950 (Scheme 1), [9a] while the potassium salt of optically active natural penicillin V, was first synthesized in 1957. [9b] The subsequent blossoming of β-lactam studies continues unabated and is well documented.<sup>[9c-e]</sup>

**Scheme 1.** Synthesis of 9-phenylpenicillin (7), [9a] and the potassium salt of natural penicillin V.

The synthesis and structure assignment by Schiff in 1864 of the first imines was an important event at the beginning of the modern age of chemistry. The finding introduced a new family of reactive organic compounds with myriad uses, including their unanticipated application in the synthesis of  $\beta$ -lactams, a major class of antibiotics, whose centenary is now being celebrated. However, the enormous potential of Schiff bases is far from exhausted and provides an endless opportunity for chemical creativity.

#### A Forgotten Man?

Schiff had a very eventful and colorful life, but outside of Italy he is little remembered today. For example, he is not mentioned in a number of recent reference works,[10] including Name Reactions and Reagents in Organic Synthesis (2005),[10a] which does cite name reactions or reagents for 55 other chemists whose family name begins with the letter S. His German-language obituaries<sup>[2a,d]</sup> were rather brief and included no photograph, whereas the obituaries in English were more extensive. [2b,c] Reasons for this neglect may be that he was an expatriate from Germany, and Italy had declared war on Germany's ally Austria-Hungary on May 24, 1915. His life and career have been widely celebrated in Italy, but this recognition has not spread elsewhere.

The life of Schiff may be compared to that of Carl Schorlemmer (1834–1892),<sup>[11]</sup> born the same year as Schiff (Figure 7). He studied in Giessen and



Figure 7. Carl Schorlemmer (1834–1892). Courtesy of the GDCh.

was also attracted to Marxism. In 1859 he immigrated in 1859 to England, where he became Professor of Organic Chemistry at Manchester in 1874 and enjoyed a successful career. Like Schiff, he engaged in studies of the aniline dyes, an important subject at the time.[11k] He was an active Marxist, referred to as "The Red Chemist",[11e] and his life has been the subject of numerous articles,<sup>[11]</sup> not only in Germany with a 16-page obituary,[11a] but also in Great Britain,[11b-e] the former communist countries of Europe, [11f-i] and in The People's Republic of China.[11j] The organic chemistry laboratory in Manchester which opened in 1895 bore his name. Later his name was also bestowed on the institute at the Technische Hochschule Leuna-Merseburg in former East Germany, and a statue of him was erected on the grounds. He was not as active an investigator as Schiff, and his continuing recognition may be attributed not only to his qualities as a chemist, but also to his position in England, where he attracted more attention than Schiff did in Italy, and to his fame as a close confidant of Marx and Engels.

The passage of time has, however, probably done the most to fade memories of Schiff, as several generations of chemists have come and gone since this exceptional individual was a familiar figure. The concept of the Schiff base is well implanted in the chemical vocabulary, but the man responsible for this highly versatile family of compounds deserves to be known in his own right. Coincidently a biographical sketch has just appeared[12] but in a journal devoted to postage stamps honoring scientists. There is no Schiff postage stamp, but the imine structure is prominently displayed on postmarks (Figure 8).[12] These ef-





*Figure 8.* Imine postmark. Courtesy of Prof. Adolfo Franchi.

forts may help to bring the man to life for the current generation of chemists.

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