

# Emil Fischer (1852–1919)

## *The Stereochemical Nature of Sugars*

James A. Magner, MD

Emil Fischer (1852–1919) made pioneering insights into the stereochemistry of the simple sugars, used the analogy of a lock-and-key fit between an enzyme and its substrate, and discovered that proteins are polypeptides. He published about organic dyes, characterized and synthesized caffeine and theobromine, and made landmark contributions regarding purines. He was awarded the Nobel Prize in Chemistry in 1902, and his work influences every endocrinologist to this day.

### A RITE OF PASSAGE

Memorizing structures of organic molecules remains a rite of passage for premedical college students studying organic chemistry. This is often a class that separates those who choose to remain premedical versus students who fall back to another college major. The situation was no different for me at the University of Illinois, Urbana, in the early 1970s. It was striking even to a novice that several simple sugars (including glucose) had the identical chemical formula,  $C_6H_{12}O_6$ , yet had different properties and biochemical roles in living tissues. The explanation rests on the nature of the asymmetric carbon atom.

The orientation of a hydroxyl (-OH) group pointing to one side or the other of these molecules makes a difference in the way enzymes interact with that sugar. Late one night, while memorizing sugar structures based on so-called “Fischer diagrams,” I read a historical note in my textbook about Emil Fischer. (My class used *Organic Chemistry*, 2nd Edition, edited by Robert Morrison and Robert Boyd, a wonderful book with a dark green cover.<sup>1</sup> Many readers may have used that squat text during that era.) I was impressed by the ingenuity, clarity, and importance of Fischer’s contribution, and I vowed someday to find out a little more about who Emil Fischer was and how he came to these wonderful insights.

As I reviewed materials to prepare this article, I was struck once again by the excellence of German science in the late 19th and early 20th centuries. This was probably in part the result of the enlightened reform of the German educational system in the 19th century, far ahead of other European countries or the United States, and the cultural emphasis on academic achievement and scientific knowledge. My reading brought to mind the apocryphal Cold War story about a U.S. official and a Soviet official arguing about which social system was better. After a few minutes, it became clear that the American official was much better informed and had extensive details about industrial production, agricultural efficiency, and so on, to back his case. Growing more and more frustrated, the exasperated Soviet official, red-faced and eyes bulging, suddenly

leaped from his chair, pounded his fist on the table, and blurted, “Our German scientists are better than your German scientists!”

### THE YOUNG EMIL FISCHER AND THE PATH TO BERLIN

Hermann Emil Fischer (Fig. 1) was born near Cologne, Germany, at Euskirchen on October 9, 1852.<sup>2,3</sup> His father ran a prosperous lumber business, and it was Emil’s good fortune throughout his life to have substantial financial resources as a result of the family enterprise. Business did not interest him, however, and his fledgling mistakes were more a signal to his father that he wanted to do something else with his life. He loved physics, but a mentor at the University of Bonn, Adolf von Baeyer (1835–1917), who had worked with August Kekulé (1829–1896; of benzene ring fame), advised Fischer in 1871 to study chemistry (von Baeyer was destined to win the Nobel Prize in Chemistry in 1905, 3 years after his student).<sup>4</sup>

After receiving his PhD in 1874, Fischer became an assistant instructor at Strasbourg University, where he discovered phenylhydrazine, the first hydrazine base. This discovery would influence his later work, for the chemical would become a useful tool for analyzing sugars. After the death of the prominent chemist Justus von Liebig in 1873, von Baeyer was invited to move to the University of Munich in 1875, and Fischer followed him there. Fischer rose to the rank of Associate Professor of Analytical Chemistry in 1879, and then

From the Genzyme Corporation, Cambridge, Massachusetts.

Reprints: James Magner, MD, Genzyme Corporation, 500 Kendall Street, 6th Floor, Cambridge, MA 02142. E-mail: James.magner@genzyme.com.

Copyright © 2004 by Lippincott Williams & Wilkins

ISSN: 1051-2144/04/1405-0239

DOI: 10.1097/01.ten.0000139005.32218.07



**FISCHER, Hermann Emil**  
Nobel Laureate CHEMISTRY 1902  
© Nobelstiftelsen

**FIGURE 1.** Emil Fischer in 1902 near the time that he was awarded the Nobel Prize in Chemistry. Copyright, The Nobel Foundation.

was appointed Professor of Chemistry in 1881 at the University of Erlangen.

He was approached in 1883 to take the position of scientific director at a private firm, Badische Anilin- und Soda-Fabrik, which we in the United States today would better recognize as BASF (founded in 1865).<sup>5</sup> This was a major opportunity for Fischer. Graebe and Lieberman at BASF had synthesized alizarin, a red dye for clothing, to compete with the natural product, “madder,” in 1869. The company then lavished funding over the next 2 decades in a focused but high-risk effort to discover a synthetic indigo. This triumph was accomplished in 1880, and as the blue

dye was commercialized, a disaster was perpetrated on the British in India as the demand for natural indigo declined precipitously (down to 641,000 hectares in 1896 and to 114,000 hectares by 1909). Although Fischer was tempted, he loved academic research, and the family money gave him the freedom to turn down the offer.

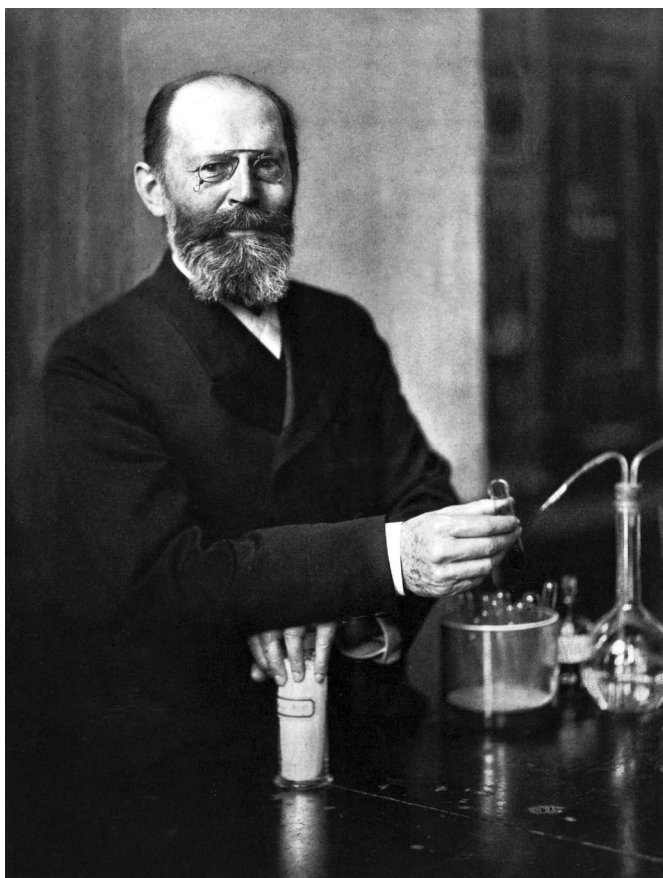
In 1887, Fischer experienced a bout of severe gastritis and took a 1-year leave of absence before moving to the University of Wurzburg. After 4 highly productive years as Professor of Chemistry there (more about glucose, see subsequently), in 1892 he made his final academic move to the University of Ber-

lin, where he succeeded A. W. Hoffman as the Chair of Chemistry. Fischer (Fig. 2) retained the Chair until his death in 1919.

### OPTICAL ACTIVITY

Jean-Baptiste Biot (1774–1862)<sup>6</sup> experimented with light, magnetism, and electricity in Paris, and discovered in 1815 that some chemicals in solution rotated the plane of polarized light, although he had no insight into the cause. The young Louis Pasteur (1822–1895),<sup>7</sup> while pursuing his first important experiments in the late 1840s, noted that the tiny crystals of tartaric acid (a key chemical present in French wine) seemed to come in 2 varieties. Using a magnifying glass, Pasteur observed that the shapes of the 2 crystal types appeared to be mirror images of each other. He tediously used tweezers to separate the 2 types of crystals and found that when dissolved, a solution of 1 type of crystal rotated polarized light in 1 direction, whereas a solution of the other type of crystal rotated polarized light in the opposite direction. Pasteur’s insight was that the molecule of tartaric acid must come in 2 forms that were mirror images of each other, like right and left gloves. However, structural chemistry was not yet advanced enough to allow Pasteur to associate this finding with bonds to carbon. (Years later, Fischer mentioned Pasteur’s experiments in his Nobel Prize lecture.)<sup>8</sup>

During the early 1870s, Jacobus H. van’t Hoff (1852–1911) and J. A. Le Bel independently came on the concept of the asymmetric carbon atom.<sup>9</sup> Although his doctoral thesis in 1874 dealt with cyanoacetic acids and malonic acid, van’t Hoff’s early fame actually derived from a small pamphlet that he published a few months before entitled “Voorstel tot Uitbreiding der Tegenwoordige in de Scheikunde gebruikte Structuurformules in de Ruimte” and so on. (“Proposal for the Development of 3-Dimensional Chemical Structural Formulae”). Consisting of 12 pages of text and 1 page of diagrams, the paper



**FIGURE 2.** Emil Fischer a few years after receiving the Nobel Prize in Chemistry. Copyright, Science Museum/Science & Society Picture Library.

showed that the asymmetric carbon atom could explain the occurrence of isomers of compounds despite their identical chemical formulae. van't Hoff also explained how such stereochemistry could be related to optical activity. These revolutionary ideas began to find acceptance the next year after publication of "Chimie dans l'Espace" ("Chemistry in Space"), although the German translation did not appear until 1877 and the English in 1891. He later acknowledged in "Dix Années dans l'Histoire d'une Théorie" ("Ten Years in the History of a Theory") that J. A. Le Bel had independently arrived at the identical concepts, although without pragmatic detail. The first publication about the asymmetric carbon atom occurred just as Fischer was finishing his doctorate. (van't Hoff later was awarded the Nobel

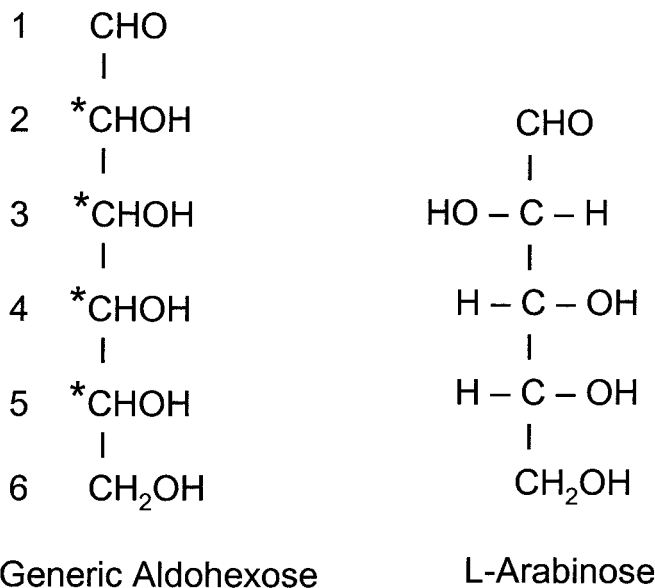
Prize in Chemistry in 1901.) The assignment as a D- or L-sugar began based on whether the plane of polarized light was rotated to the right or left (dextrorotary or levorotary). Today, optical isomers of monosaccharides are assigned as either D- or L- based on their absolute configurations as relative to D-glyceraldehyde, as proposed by Rosanoff, an American chemist, in 1906.<sup>1</sup>

### A FAMILY OF ALDOHEXOSES

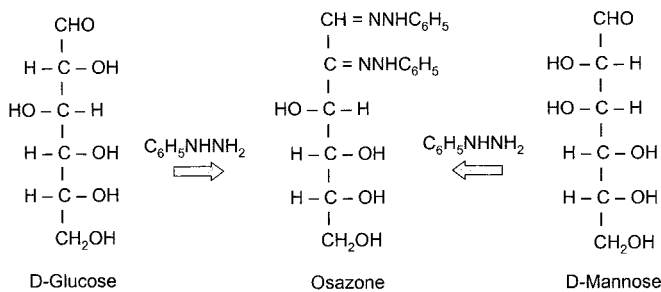
As shown in Figure 3, the structural formula for an aldohexose (such as glucose) contains 4 asymmetric carbon atoms, each marked by an asterisk.<sup>1</sup> Thus, there are 2<sup>4</sup> or 16 possible stereoisomers having this general formula, 8 pairs of enantiomers, as we would say today. This is the family of aldohexoses.

All 16 compounds have been created by synthesis or isolated from nature, and include the very common compounds glucose, mannose, and galactose (each with a D- and an L-form). The generic structural formula as drawn in Figure 3 could represent any of the aldohexoses. Only when one has specified the configuration about each of the asymmetric carbon atoms will the formula refer to a unique aldohexose. The carbon atoms are numbered in Figure 3 from the "top" downward in the usual convention. A specific natural 5-carbon sugar, L-arabinose, which will play an important part in this story, is depicted to the right in Figure 3. Note that the 5 carbon atoms in L-arabinose correspond to carbons 2 through 6 of the generic aldohexose formula. Another caveat is that in these types of diagrams, the bonds on a given carbon atom depicted horizontally by convention are meant to be projecting out from the page, whereas the vertical bonds are projecting into the page.<sup>1</sup>

The way that Fischer worked out the correct configurations of the aldohexoses demanded years of trial and error, ingenuity, and logic. We return now to the reagent phenylhydrazine, which Fischer discovered early in his career. Aldoses react with this compound to form phenylhydrazones, and when both the first and second carbon have reacted, the product is called an osazone<sup>1</sup> (Fig. 4). Note the loss of asymmetry about carbon 2 after this reaction, because there are now only 3 atoms bound to that carbon instead of 4. Moreover, 1 of the difficulties of studying monosaccharides was their tendency to form syrups rather than solids that could be dissolved and crystallized easily. While working at the University of Munich in the early 1880s, Fischer found that his reagent, phenylhydrazine, converted sugars into osazones that could be isolated easily, and their crystals had characteristic forms that could be identified. Fischer found that 2 distinct monosaccharides, D-glucose and D-mannose, yielded the same osazone. Because osazone formation destroyed



**FIGURE 3.** Generic structure of an aldohexose (left) such as glucose or mannose. The conventional numbering of the carbon atoms is shown, and the 4 asymmetric carbons are marked with asterisks. Correct structure of L-arabinose (right). Fischer determined this structure as a stepping stone on the way to learning the structure of glucose. Fischer discovered and then built on the fact that the 5 carbons in L-arabinose correspond to carbons 2 through 6 in glucose.



**FIGURE 4.** Structures of D-glucose, D-mannose, and their common osazone. Fischer discovered that after reacting D-glucose or D-mannose with phenylhydrazine, the asymmetry of carbon 2 was destroyed, and these 2 sugars formed the identical osazone. Although at first Fischer did not know the configurations at carbons 3, 4, and 5, he knew at that stage that these configurations would turn out to be identical in D-glucose and D-mannose. The configuration at carbon 5 was assumed to have the -OH to the right (this arbitrary assumption was found to have been correct only years later when absolute configurations could be established). Then Fischer deduced the relative configurations about carbons 3 and 4 by studies of L-arabinose. Finally, the correct configuration at carbon 2 was assigned after complex studies of D-glucose.

asymmetry about carbon 2 without changing the configuration of the rest of the molecule, it followed logically that D-glucose and D-mannose were identical (but still with unknown structures at this point) except that they had configurations about carbon 2 that were mirror

images (Fig. 4). Today we call D-glucose and D-mannose epimers.<sup>1</sup>

### A CHAIN OF LOGIC TO THE STRUCTURE OF D-GLUCOSE

In 1886, Heinrich Kiliani at the Technische Hochschule in Munich dis-

covered a method for lengthening the carbon chain of sugars (the added carbon was at the “top” of the chain, as oriented in the figures—an important detail).<sup>1</sup> Fischer extended that method with a reduction step to be able to study the reaction products as aldoses, the so-called Kiliani-Fischer synthesis.<sup>1</sup> Fischer knew that D-glucose, the most important monosaccharide, was an aldohexose, and in 1888 he set out to learn which of the 16 possible configurations of C<sub>6</sub>H<sub>12</sub>O<sub>6</sub> was the correct formula for naturally occurring glucose. Fischer took as a necessary arbitrary starting assumption that the -OH group of D-glucose at carbon 5 was on the right side, and he then worked out the relative configurations about the other carbon atoms. Thus, he was determining (by internal consistency of all of the classic chemical reactions) which of 8 possible structures represented D-glucose. We know today, now that absolute configurations can be established, that the -OH group at carbon 5 of D-glucose actually is on the right side, so Fischer happens to have guessed correctly in terms of the absolute configuration.

The path that Fischer took to learn the structure of D-glucose remains a complicated one to explain, so I will only mention the highlights here, and the interested reader wanting additional details will need to peruse Chapter 33 in Morrison and Boyd.<sup>1</sup> Fischer started by deciphering the correct configuration of the 5-carbon sugar, L-arabinose (Fig. 3). He found that oxidation of L-arabinose yielded a product that was optically active, implying that if the -OH group on the last asymmetric carbon was assumed to be on the right side, then the -OH group 2 carbons away was on the left side (or else there would have been no optical activity). Thus, these L-arabinose data provided the detail that in D-glucose, carbon 3 had a -OH group on the left.

Fischer next found that L-arabinose was converted in the Kiliani-Fischer synthesis (by adding a carbon to the “top”) into both D-glucose and

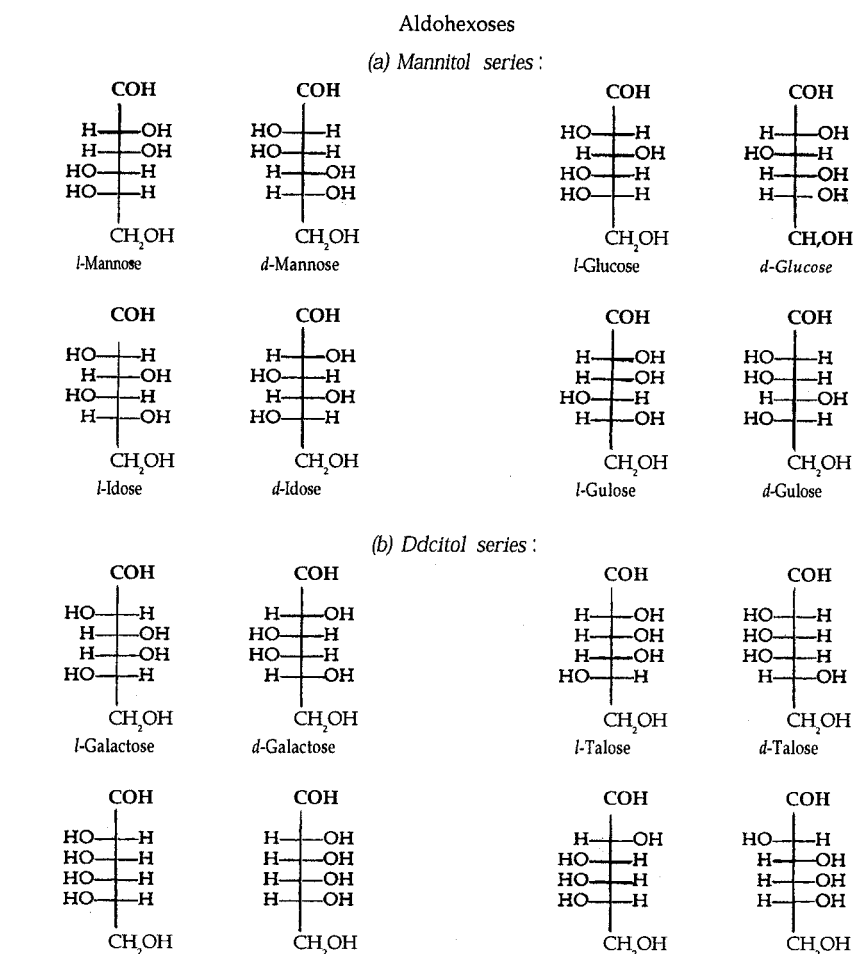
D-mannose. These 2 sugars, therefore, must have the same configurations about carbons 3, 4, and 5 as did the analogous carbons in L-arabinose. Fischer then discovered that, when oxidized by acid, both D-glucose and D-mannose yielded dicarboxylic acids that were optically active, implying that the -OH group on carbon 4 is on the right side (because if it had been on the left side, one of the resulting compounds would not have been optically active). This established that the analogous carbon in L-arabinose must have had the -OH group on the right side, which established the correct formula for L-arabinose.

Finally, Fischer determined that the oxidation of another hexose, D-glucose (which he was required to synthesize), yielded the same dicarboxylic acid as did oxidation of D-glucose. A somewhat complex chain of logic based on this observation established that the -OH on carbon 2 in D-glucose must be on the right side. It followed that the correct structure of D-glucose must be as shown in Figure 4, with D-mannose having the opposite configuration about carbon 2.

Fischer published<sup>10</sup> this result in 1891 while at the University of Wurzburg, and this triumph of determination and logic was primarily responsible for his being awarded the Nobel Prize in Chemistry in 1902, although he was also well known by that time for his landmark work on purines. During his Nobel Lecture,<sup>8</sup> delivered on December 12, 1902, he proudly showed the structures of a family of purines and made several jokes about wonderful compounds that had come from foul-smelling substances such as guanine from guano. He also showed the 16 formulae of the aldohexoses (Fig. 5), of which only 12 substances had actually been synthesized or isolated from nature at that time.

### PROTEINS ARE POLYPEPTIDES

During the early 20th century, Fischer turned his attention to identifying the individual amino acids and was the discoverer of proline. He coined



**FIGURE 5.** Figure used by Emil Fischer in his Nobel Prize lecture of December 12, 1902, to illustrate the 16 structures of the family of aldohexoses. Copyright, The Nobel Foundation.

the term “peptide bond.” Fischer then started with individual purified amino acids and synthesized short peptides. He also studied enzymes and fats, and even analyzed lichen brought back from Black Forest holidays. In 1902, at the meeting of the Society of German Scientists and Physicians in Karlsbad, Fischer followed the eminent chemist Franz Hofmeister (1850–1922) on the program. Hofmeister presented a plenary lecture about the possible structure of proteins; then Fischer spoke about the isolation of amino acids from protein hydrolysates and suggested that proteins were made from amino acids linked together. Thus was born the Fischer-Hofmeister theory of protein structure.

### PERSONAL LIFE

A brilliant and patient man, Fischer is said to have had a keen memory, and he made up for his poor speaking ability by being able to memorize many pages of lecture notes. In 1888, Fischer married Agnes Gerlach, who was the daughter of the anatomy professor at Erlangen. Although she died in the seventh year of their marriage, they had 3 sons. Unhappily, 1 was killed in the First World War, and another took his own life at age 25 while distraught over compulsory military service. A third son, Hermann Otto Laurenz Fischer (died 1960), eventually became a Professor of Biochemistry at the University of California

at Berkeley. In the early years of World War I, Emil Fischer is said to have been a patriot, but later became disenchanted with Germanic folly. Shortly after the war, his health failed, possibly as a result of chronic exposure to multiple chemical solvents, and it is believed that he developed a type of cancer. Amid the shambles of postwar Germany, these problems overwhelmed him and it is believed that he took his own life<sup>11</sup> in 1919.

### THE LEGACY

Shortly after Fischer's death, the German Chemical Society established the Emil Fischer Memorial Medal, viewed as a prestigious scientific award. The field of carbohydrate chemistry moved onward. In the 1890s, Fischer himself had provided evidence that glucose actually was a cyclic structure, and Tollens, Tanret, and many others contributed to this concept.<sup>1</sup> In 1909, C. S. Hudson of the U.S. Public Health Service made proposals about nomenclature that were widely accepted (and the enantiomer of alpha-D-[+]-glucose became alpha-L-[-]-glucose), although in 1926 the ring size was corrected.<sup>1</sup> The -OH groups pointing to the right in Fischer diagrams were agreed to be pointing downward in the cyclic structures. Although some of these conven-

tions were initially based on questionable relationships postulated to exist between configuration and optical rotation, subsequent enzymatic and x-ray evidence have bolstered the choices made.

Emil Fischer was an inspiration to students and colleagues. He made many fundamental contributions to modern biochemistry that we take for granted today. He had a special influence on me, apparently, after I read about his diagrams in college. That lesson may have predisposed me, perhaps, to have a bit of extra interest in carbohydrate biochemistry. When chance factors years later provided certain opportunities for me, I chose to study the oligosaccharides of the glycoprotein hormones. A few months ago my office moved to a new building in which the conference rooms were being named for famous scientists, and Fischer was selected to be so honored. This coincidence prompted me to keep my promise from decades before—to find a few minutes to learn more about this remarkable man's life.

### REFERENCES

- Morrison RT, Boyd RN, eds. *Organic Chemistry*. 2nd ed. Boston: Allyn and Bacon; 1969.
- Emil Fischer—Biography (official web site of the Nobel Foundation). January 30, 2004. Available at: <http://www.nobel.se/chemistry/laureates/1902/fischer-bio.html>. Accessed April 19, 2004.
- Hermann Emil Fischer 1852–1919 (web site of Peptides International). Available at: <http://www.pepnet.com/fischerbio.html>. Accessed April 19, 2004.
- Adolf von Baeyer—Biography (official web site of the Nobel Foundation). June 23, 2003. Available at: <http://www.nobel.se/chemistry/laureates/1905/baeyer-bio.html>. Accessed April 19, 2004.
- Lecture 5: Organic Chemistry & International Politics (web site of University of Toronto). Available at: <http://www.chass.utoronto.ca/~bhall/hps282f/LECTURE%205%20Organic%20Chemistry.html>. Accessed May 7, 2004.
- Jean-Baptiste Biot (web site of School of Mathematics and Statistics, University of St. Andrews, Scotland). January 1997. Available at: <http://www.history.mcs.st-andrews.ac.uk/Mathematicians/Biot.html>. Accessed May 5, 2004.
- Geison GL. *The Private Science of Louis Pasteur*. Princeton, NJ: Princeton University Press; 1995.
- Emil Fischer-Nobel Lecture (official web site of the Nobel Foundation). April 7, 2004. Available at: <http://www.se/chemistry/laureates/1902/fischer-lecture.html>. Accessed April 19, 2004.
- Jacobus H. van't Hoff—Biography (official web site of the Nobel Foundation). April 15, 2004. Available at: <http://www.nobel.se/chemistry/laureates/1901/hoff-bio.html>. Accessed April 19, 2004.
- McBride JM. Emil Fischer: On the configuration of grape sugar and its isomers. I. Classic paper as first published in *Berichte d d chem Gesellsch* 24:1836 (1891) (web site of J. M. McBride, Yale). Available at: <http://classes.yale.edu/chem125a/125/history99/6Stereochemistry/Fischer/FischerGlucosePrf.pdf>. Accessed May 6, 2004.
- Reynolds R, Tanford C. Enzyme action. Emil Hermann Fischer 1852–1919. In: Tallack P, ed. *The Science Book*. London: Weidenfeld & Nicolson; 2003:218–219.