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## Emil Fischer's Proof of the Configuration of Sugars: A Centennial Tribute\*\*

By Frieder W. Lichtenthaler\*

Today's textbooks convey the deceptive impression that chemistry developed in a rational and orderly process with discoveries following one upon another in a vertical progression—an impression that tends to classify Fischer's achievement as a matter-of-fact historical development. This misconception does not consider the instances of serendipity invariably involved, and entirely fails to appreciate the human endeavor, the intellectual struggle of the dedicated researcher, and the forging force of his personality that eventually led to this key insight. The hundredth anniversary of Fischer's classical piece of work provides a welcome opportunity not only to highlight its paramount importance for the development of carbohydrate chemistry, and of organic chemistry in general, but to trace the creative processes underlying this fundamental discovery, the thought patterns at a conceptual level, and the constructive reasoning that eventually led to it. Their understanding and appreciation is essential for emulating Fischer's achievement in a modern context.

*Die Geschichte einer Wissenschaft  
ist diese Wissenschaft selbst*  
J. W. von Goethe<sup>\*\*\*</sup>

The rapid pace and volume of scientific discoveries tend to eclipse not only those of past decades, but those of the past century in particular. This leads to a gross underestimation of the basic contributions of the pioneers of our science who laid the very foundations of current research. Pertinent examples of this are the foundation of organic structural chemistry and the proposal of the benzene formula by Kekulé in 1865<sup>[1]</sup> and, ten years later, the postulation of tetrahedral

geometry for carbon by Le Bel and van't Hoff,<sup>[2, 3]</sup> which provided an explanation for the occurrence of numerous isomers inexplicable on the basis of the then current structural formulas. Another case in point, substantially undervalued in its impact on the development of organic chemistry, is the establishment of the relative configurations of the sugars by Emil Fischer in 1891,<sup>[4, 5]</sup> a most remarkable piece of research which not only put carbohydrate chemistry on a rational basis but—more importantly for that time—provided unequivocal proof for the validity of the Le Bel–van't Hoff theory of stereoisomerism.

The essence of what was to become the sugar family tree, and what inaugurated a new mode of writing stereoformulas is contained in two publications by Fischer (Fig. 1) in the *Berichte der Deutschen Chemischen Gesellschaft*, the first appearing in the September issue of 1891<sup>[4]</sup> (Fig. 2) and the second only two months later.<sup>[5]</sup> Both papers carried the

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This account is dedicated to Professor Klaus Hafner on the occasion of his 65th birthday; his exemplary tribute to Kekulé on his 150th birthday gave the essential impulses to this centennial.

[\*\*\*] "The history of a science is the science itself."



Fig. 1. Emil Fischer (1852–1919) in 1889 [6].

modes title “Über die Configuration des Traubenzuckers und seiner Isomeren” (On the Configuration of Grape Sugar and its Isomers), yet the introductory sentence of the first of these (see Fig. 2) gives a clear indication of the fundamental question to be addressed, and the solution that was achieved:

“All previous observations in the sugar group are in such complete agreement with the theory of the asymmetric carbon atom, that, by now, one may dare to use this theory as a basis for the classification of those substances.”

This not only announced the advent of a rational sugar chemistry but, de facto, that of applied organic stereochemistry as well; the discovery was to shape the development of organic chemistry to an extent that can be compared only with the impact that Kekulé’s benzene formula<sup>[6]</sup> had made 25 years earlier.

Modern textbooks give the deceptive impression that chemistry developed in a rational and orderly way in which discoveries follow one after another in a vertical progression—an impression that tends to classify Fischer’s achievement as purely an historical development, accomplished by some remote, legendary historical figure. This misconception does not consider the instances of serendipity invariably involved, and entirely fails to appreciate the human endeavor, the intellectual struggle of the dedicated researcher, and the forging force of his personality that eventually led to this key insight. The hundredth anniversary of this classical piece of work provides a unique opportunity not only to highlight and appraise its paramount importance for the development

**295. Emil Fischer: Ueber die Configuration des Traubenzuckers und seiner Isomeren.**

[Aus dem chemischen Laboratorium der Universität Würzburg.]

(Eingegangen am 6. Juni.)

(Vorgetragen von Hrn. Tiemann.)

Alle bisherigen Beobachtungen in der Zuckergruppe stehen mit der Theorie des asymmetrischen Kohlenstoffatoms in so vollkommener Übereinstimmung, dass man schon jetzt den Versuch wagen darf, dieselbe als Grundlage für die Klassification dieser Substanzen zu benutzen. Die Theorie lässt sechzehn Isomere von der Struktur des Traubenzuckers voraussehen. Diese Zahl reducirt sich auf zehn für ihre Derivate, deren Molekül symmetrisch ist.

Die folgende Tabelle, welche der Broschüre von van’t Hoff-Herrmann: »Die Lagerungen der Atome im Raum« Seite 11 entnommen ist, enthält die sechzehn verschiedenen Formen für die Zucker, wovon die Nummern 11–16 identisch werden mit 5–10 bei den sechsverthigen Alkoholen und zweibasischen Säuren:

	11	12	13	14	15	16
+	+	+	+	+	+	-
+	+	+	-	-	-	+
+	+	-	-	+	-	-
+	-	+	-	-	-	-
+	-	+	-	+	-	-
+	+	-	-	-	-	+
1	2	3	4	5	6	7
				8	9	10

Um nun an der Hand der Tatsachen die dem Traubenzucker zugehörige Form auszuwählen, ist es zunächst nötig, die Zuckersäure zu betrachten. Von derselben sind die beiden optisch entgegengesetzten Formen bekannt; ferner entsteht die *d*-Zuckersäure einerseits aus dem Traubenzucker (*d*-Glucose) und andererseits aus der stereoisomeren *d*-Gulose.

Daraus geht hervor, daß die beiden Zuckersäuren unter die Nummern 5–10 fallen müssen; denn nur diese können aus je zwei stereoisomeren Zuckern entstehen.

Unter diesen sechs Nummern sind aber zwei optisch inaktive Systeme (7 und 8), welche mithin wegfallen.

Endlich können noch die Nummern 6 und 10 durch folgende Betrachtung ausgeschlossen werden. Glucose und Mannose unterscheiden sich nur durch die verschiedene Anordnung an dem asymmetrischen Kohlenstoffatom, welches in der nachstehenden Formel mit \* bezeichnet ist:

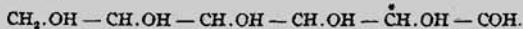
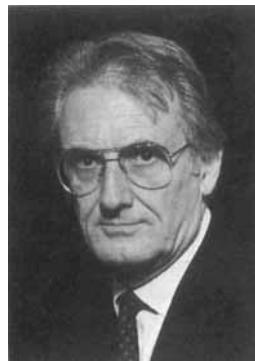


Fig. 2. Title page of the first [4] of Fischer’s two landmark papers in 1891 on the configuration of sugars.

of organic stereochemistry in general, and carbohydrate chemistry in particular—this has been done, over the years, in many specialized accounts<sup>[7–14]</sup>—or for keeping pivotal facts from oblivion. During the past hundred years there has been almost unbelievable material and conceptual progress; what has not changed, however, are the creative processes underlying a fundamental discovery and the constructive reasoning that eventually led to it. Their understanding and



Frieder W. Lichtenthaler, born 1932 in Heidelberg, studied chemistry at the University of Heidelberg from 1952–1956 and received his doctorate there in 1959 under F. Cramer for research on enol phosphates. The following three years he spent as a postdoctoral fellow at the University of California, Berkeley, with Hermann O. L. Fischer—the only of Emil Fischer’s three sons who survived the first World War.<sup>[10a]</sup> He subsequently worked as an assistant at the Technische Hochschule Darmstadt, where he acquired his “Habilitation” in 1963, was appointed associate professor in 1968, and was promoted to full professor in 1972. His research activities center on the generation of enantiopure building blocks from sugars, their utilization in the synthesis of oligosaccharides and complex non-carbohydrate natural products, the computer simulation of chemical and biological properties of sugars, and studies towards the utilization of carbohydrates as organic raw materials.

appreciation is required to emulate Fischer's achievement in a modern context.

The attempt to trace these processes starts with the analytical reagent which Fischer was the first to use in carbohydrate chemistry in 1884, and with which he established the relative configurations of the sugars only seven years later: *phenylhydrazine*, a base, which he accidentally discovered in 1875 at the age of 23, while working as an assistant in Baeyer's Strassburg laboratory. The resulting publication<sup>[15]</sup> (Fig. 3) is unusual in several respects. First, Baeyer, in whose institute the work was done, allowed him to publish it on his own; that there isn't even an acknowledgement to his teacher attests to the seemingly high esteem and encouraging attitude Baeyer had for his gifted pupil; second, the paper is formulated in a concise, clear style undoubtedly adopted from his teacher, and written in the first person. For example, in the paper reproduced in Figure 3, he writes,

"I have again taken up experiments on the reduction of diazo compounds. ... I arrived at a class of well-characterized bases, for which I propose the name hydrazine compounds".

A rather self-confident statement for a young chemist who had just received his doctorate, and the more so as the parent compound, hydrazine, was discovered only twelve years later, in 1887, by Curtius.<sup>[16]</sup> Reading Fischer's paper of 1875 today engenders the sensation of contemplating the modest source of what was to become a mighty river within the next 15 years.

The research school of Adolf Baeyer (1835–1917<sup>[17]</sup>), from which Fischer emerged—first in Strassburg, and then

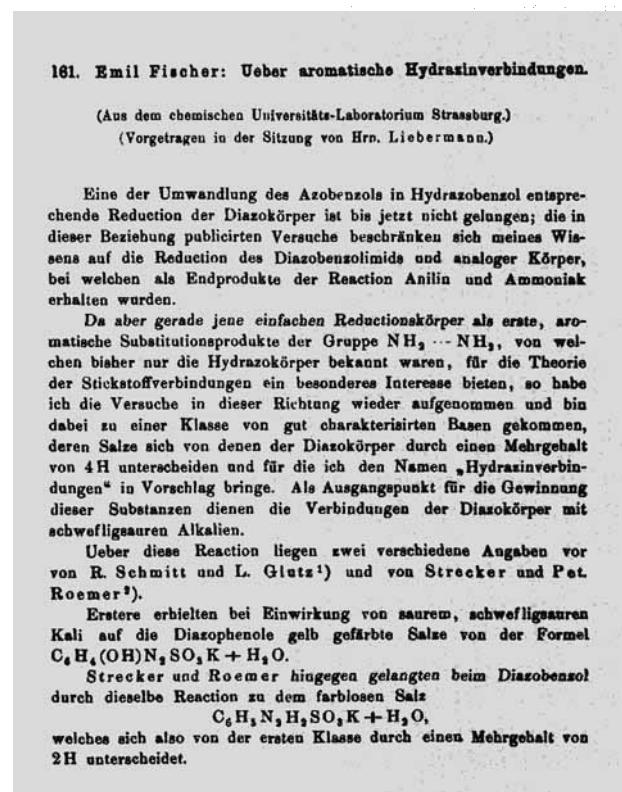


Fig. 3. Title page of Fischer's 1875 paper on the discovery of phenylhydrazine [15].

for 40 years after 1875 at the University of Munich—was a major “forge” of talent. A group photograph<sup>[18]</sup> of 1878 attests to that almost literally: the unusually wide hood in the background is certainly more reminiscent of a forge than of a laboratory. In the center Adolf Baeyer, wearing a prominent hat; since several others also wear headgear, we may deduce that in the winter of 1878 the heating was deficient in that laboratory. To the right of Baeyer the 25-year-old Emil Fischer, in a peaked cap and strikingly self-confident three years after his Ph.D.; to the left Jacob Volhard (1834–1910), who was in charge of the analytical division in Baeyer's institute, and whose successor Fischer was to become in Munich a year later (1879), and at the University of Erlangen in 1882. Far to the left Fischer's cousin Otto Fischer, with whom he did extensive work on rosaniline dyes.<sup>[20]</sup> Between Baeyer and Volhard stands Wilhelm Koenigs (1851–1906<sup>[21]</sup>) who in 1900, together with his co-worker Eduard Knorr, discovered the  $\text{Ag}_2\text{CO}_3$ -induced glycosidation of acetobromoglucose,<sup>[22]</sup> known today as the Koenigs–Knorr reaction.

A survey of the early papers of Emil Fischer indicates the curious fact that although the ability of phenylhydrazine to react with aldehydes was quickly observed by him—the phenylhydrazone of acetaldehyde, benzaldehyde, and furfural were unequivocally characterized and structurally secured<sup>[23]</sup>—Fischer does not appear to have recognized the tremendous values of the compound for the characterization and identification of carbonyl compounds until nearly 10 years later, in 1884,<sup>[24]</sup> when he finally applied it to the sugars. This ‘induction period’ had several reasons:

Over a number of years (1876–1880) he did extensive investigations on rosaniline dyes with his cousin Otto Fischer.<sup>[20]</sup>

He pursued his habilitation and completed it in the spring of 1878.

In the fall of 1878, he took charge of the analytical division of Baeyer's institute, as the successor to J. Volhard.

In 1881 he started work on purines, investigating the structure caffeine. Although he initially devised an erroneous formula,<sup>[25]</sup> the research eventually led to his classification of purines.

In 1882 at the age of 30, he moved from Munich to Erlangen, accepting the chair of chemistry at that university, and there he was intensely occupied with the conversion of phenylhydrazine into N-heterocycles,<sup>[26]</sup> which led to the Fischer indole synthesis.<sup>[27]</sup>

Another reason for not applying phenylhydrazine to sugars earlier, although their “aldehyde nature” was known, may have been the desolate state in which the chemistry of sugars was at that time. Because of the nature of these substances, their study was fraught with great difficulty, especially since impure sugars tend to form syrups, which in the second half of last century could not be analyzed reliably. A compound had to be crystalline, and be recrystallizable to a constant melting point and optical rotation to be considered pure. Thus, it is not surprising that early progress in the field of carbohydrates could not be achieved, whereas, for example, the chemistry of the aromatic compounds was well-developed.

Around 1870, chemists recognized two aldohexoses, glucose and galactose, and one ketose (levulose, later named



Fig. 4. Photograph of the Baeyer group in 1878 at the laboratory of the University of Munich (room for combustion analysis), with inscriptions from Fischer's hand [18].

fructose by Fischer). Three disaccharides, sucrose, lactose, and maltose were also characterized as distinct compounds. The experimental evidence for their structures was very scarce, yet it had gradually led to the assumption that they may be straight-chain pentahydroxyaldehydes. Thus, A. Baeyer in an 1870 Berichte paper<sup>[28]</sup> expressed the opinion:

"On the basis of all known experience the constitution of grape sugar must correspond to one of the two formulas [shown in Fig. 5 (top left)], or at least be very closely related thereto."

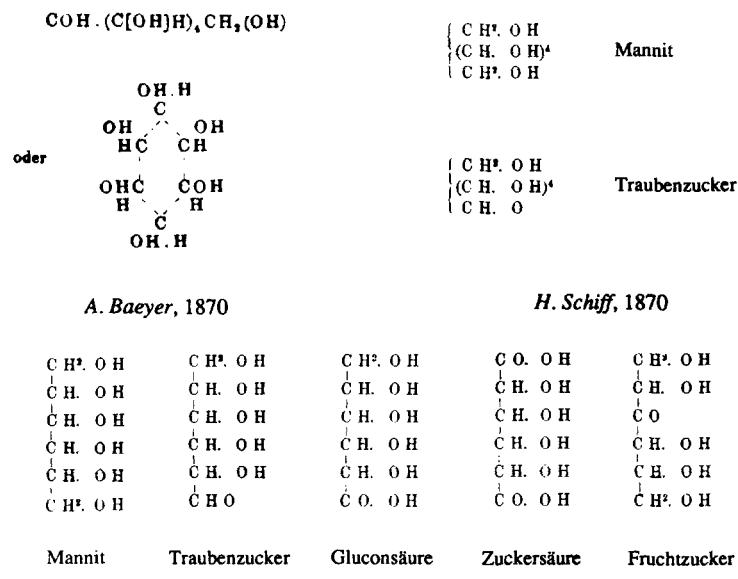
Hugo Schiff, in the same year, formulated "grape sugar as the first aldehyde of mannitol" (Fig. 5 top right).<sup>[29]</sup> The most elaborate formulations (Fig. 5 bottom) stem from Rudolph Fittig (1835–1910) in 1871:<sup>[30]</sup>

"Grape sugar is the aldehyde of mannitol, and mannitol is the saturated sixfold acidic alcohol of hexane. On gentle oxidation of grape sugar, like with all other aldehydes, the CHO group is converted into carboxyl COOH, and a uni-

basic acid of six atoms  $C_6H^{12}O^7$ , gluconic acid, is formed. Since gluconic acid contains a second oxidizable  $CH^2OH$  group, further oxidation must result in a dibasic acid. This acid is sugar acid, which contains four hydroxyl atoms apart from the two carboxyl groups."

Fittig's formulas (Fig. 5 bottom) did not show any stereochemical relationships of the various hydroxyl groups, and thus many reactions of the sugars were far from being understood.

This explains why, in the course of the 15 years following, very little progress was made either experimentally or conceptually. The interrelationships of the sugars remained something of a black box, except maybe for the fact that in 1883 Tollens (Fig. 6)<sup>[31]</sup> intuitively anticipated the cyclic hemiacetal forms of sugars, without, of course, fully realizing their significance (see Fig. 7): glucose ("Dextrose") forms a seven or five-membered ring, fructose ("Laevulose") was thought to adopt the furanoid form, which happens to be the one realized in sucrose ("Rohrzucker").



*R. Fittig, 1871*

Fig. 5. Structural concepts on sugars around 1870 by Adolf Baeyer [28], Hugo Schiff [29], and Rudolph Fittig [30].

A year after Tollens's intuitive foresight, that is, in 1884, Emil Fischer began his studies with sugars and phenylhydrazine. He found that when heated with this base, glucose and fructose yielded the same, beautifully crystalline compound, which, unlike the free sugars, was readily characterizable; it was designated "phenylglucosazone". Fischer noted that the course of the reaction with these sugars was decisively different from that of standard aldehydes, but understandably, the individual steps of the osazone formation were not clear initially.<sup>[24]</sup> He formulated only the stoichiometric equation (Fig. 8 top) with the commentary "I cannot say anything definite yet on the fate of the two hydrogen atoms".

In an ensuing paper from 1887,<sup>[32]</sup> Fischer discovered the intermediate phenylhydrazone by performing the reaction in the cold. Thus, he was able to supply the necessary information for deducing the correct constitutional formula (Fig. 8 bottom).<sup>[32]</sup>

These hydrazones and osazones have not only rendered invaluable service for the identification and isolation of the

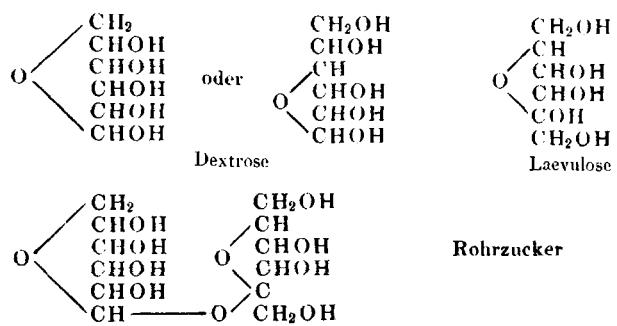


Fig. 7. Tollens' 1883 conception of cyclic hemiacetal formulas for glucose ("Dextrose"), fructose ("Laevulose"), and sucrose ("Rohrzucker") [31].

then existing sugars, but also have been instrumental in the preparation of new ones. At this early stage of his studies, in 1887, Fischer discovered a new hexose in this way: gentle oxidation of mannitol with nitric acid and exposure of the resulting mixture to phenylhydrazine led to a phenylhydrazone, isomeric with the one generated from glucose. By the acid hydrolysis of this product he obtained an as yet unknown hexose, which he named mannose.<sup>[33]</sup> This study soon led to an important conceptual result: glucose and

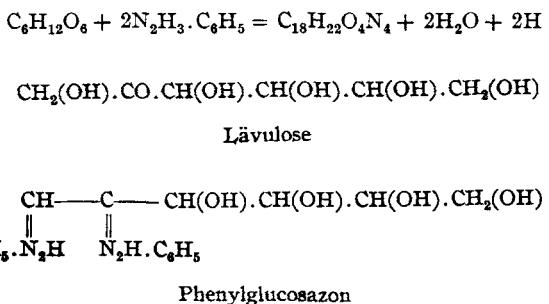


Fig. 8. Formation of osazones from glucose and fructose ("Lävulose") [24, 32].

mannose yield different hydrazones but the same osazone (Fig. 9), hence they must be 2-epimeric aldoses. For the rationalization of these data Fischer, in a 1889 paper with Hirschberger,<sup>[34]</sup> made use of the Le Bel-van't Hoff theory for the first time:

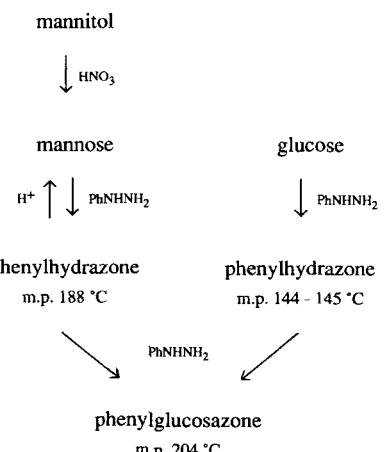


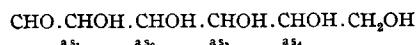
Fig. 9. Glucose and mannose yield the same osazone.



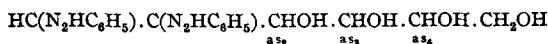
Fig. 6. Bernhard Tollens (1841–1918) in 1890 [6].

"In the sugar group, dextrose and mannose are the first examples of two isomers, which have the same structure and can be converted into each other. For the explanation of this form of isomerism, we draw entirely on the principles of the Le Bel-van't Hoff theory.

The formula contains four asymmetric carbon atoms, which we find appropriate to differentiate by the designations as<sub>1</sub>, as<sub>2</sub>, as<sub>3</sub>, and as<sub>4</sub>:



Each of these carbon atoms causes the existence of two geometric isomers, yielding no less than 16 isomers predicted by theory. From the experimental material at hand it can now be easily proved that the isomerism of dextrose and mannose is determined by carbon atom as<sub>1</sub>. The phenylhydrazones of the two sugars are distinctly different, yet with particular ease they give the same osazone with the structural formula



in which carbon as<sub>1</sub> has lost its asymmetry. Since it is highly improbable that the carbon atoms as<sub>2</sub>, as<sub>3</sub>, and as<sub>4</sub> change their steric arrangements during the smooth and particularly easy osazone formation, one must assume that the difference between mannose and dextrose rests on the asymmetry of carbon atom as<sub>1</sub>."<sup>[34]</sup>

The accessibility of mannose was soon greatly improved by its discovery in nature, first in salep mucilage<sup>[35]</sup> and then in the seeds of the tagua palm,<sup>[36]</sup> also known as ivory nut, at the time a commercial product used to make buttons. Ivory nut turned out to be a mannose polysaccharide, which yielded a sugar on acid hydrolysis that was identical with the product obtained by gentle oxidation of mannitol (Fig. 10). By further oxidation with bromine water the corresponding aldonic acid was prepared, whilst more rigorous oxidative conditions (HNO<sub>3</sub>) led to the aldaric acid, which on the basis of their derivation were named mannonic and mannaric acid, respectively:<sup>[37]</sup>

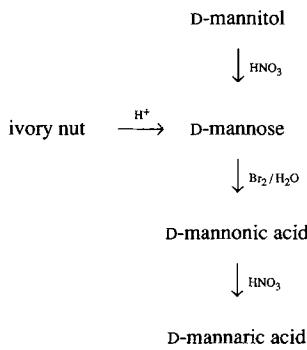


Fig. 10. Elaboration of the ensuing chemistry of mannose after it became available on a large scale by the acid hydrolysis of ivory nut shavings [37, 38].

The experimental difficulties encountered in this type of work because of the techniques available around 1890 were formidable, which made great demands on the experimental

skill and patience of Fischer's Ph.D. students who carried out the work. The following excerpt from a letter of Fischer's to his mentor and friend A. Baeyer, dated January 12, 1889, gives ample proof thereof:<sup>[39]</sup>

"The investigations on sugars are proceeding very gradually. It will perhaps interest you that mannose is the geometrical isomer of grape sugar. Unfortunately, the experimental difficulties in this group are so great, that a single experiment takes more time in weeks than other classes of compounds take in hours, so only very rarely a student is found who can be used for this work. Thus, nowadays, I often face difficulties in trying to find themes for the doctoral theses."

The research of Heinrich Kiliani (1855–1945)<sup>[40]</sup> proceeded parallel to these studies. His application of the cyanohydrin reaction for the reduction of sugars in 1885<sup>[41]</sup> was to have a major bearing on unraveling the sugar configurations. The polyhydroxy acids resulting from the hydrolysis of the hydrocyanic acid adducts contained one more carbon atom than the parent sugar, and on reduction with hydrogen iodide/red phosphorus afforded the corresponding "dehydroxylated" carboxylic acids. In this way, Kiliani established that the natural arabinose is a straight-chain aldopentose (1887)<sup>[42]</sup> and convincingly proved that glucose and galactose are aldohexoses,<sup>[43, 44]</sup> and that fructose must be a 2-ketohexose since it forms a 2-methyl-branched hexanoic acid (Fig. 11).<sup>[41]</sup>

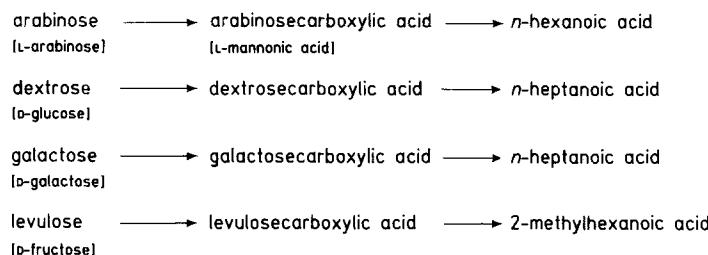


Fig. 11. Kiliani's results, 1885–1889, on the cyanohydrin extension of the sugars, and his proof of their straight-chain nature by reductive "dehydroxylation" with hydrogen iodide/red phosphorus to the corresponding alkanoic acids [41–44].

At this stage of the gradually unfolding interrelationships between the sugars in that still very "black box", an observation was made by Fischer that was to lead to a key insight: the mannonic acid obtained from mannose derived from ivory nut on gentle oxidation proved to be identical—in the form of its nicely crystalline lactone—with that obtained by Kiliani from natural arabinose by cyanohydrin extension, except for the sign of rotation<sup>[45]</sup> (Fig. 12). Consequently, the two products had to be mirror images, that is, enantiomers—a conclusion Fischer corroborated by comparing the corresponding 1,6-dicarboxylic acids, the sugars themselves, and the sugar alcohols,<sup>[44]</sup> thus providing an entire set of enantiomeric products. In an 1890 lecture Fischer attests to the conceptual importance of these results:<sup>[46]</sup>

"The observation that the mannonic acid obtained by oxidation of natural mannose is the optical isomer of ara-

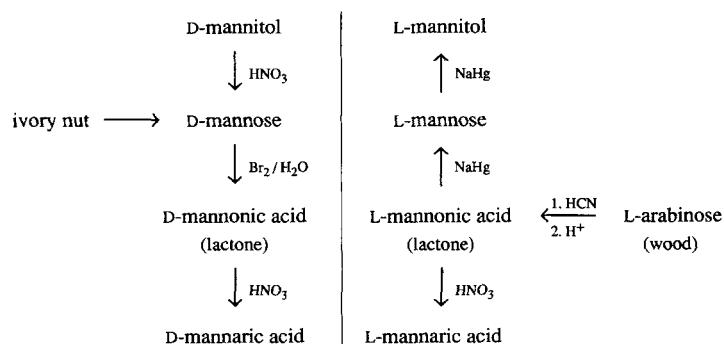


Fig. 12. Elaboration of the first complete set of enantiomers in the sugar group by Fischer [45].

binosecarboxylic acid provided the key to determining the interrelationships in the mannitol group.”

Fischer had discovered in 1889 that the lactones of sugar acids could be reduced by sodium amalgam to yield the corresponding aldoses.<sup>[47]</sup> The combination of this reduction with Kiliani’s cyanohydrin procedure, which entered the literature as the Kiliani–Fischer synthesis, did not only become a standard method for the chain extension of sugars, (Fischer applied it extensively for the preparation of heptoses,<sup>[48]</sup> octoses, and nonoses<sup>[48, 49]</sup>), but more important for the time around 1890, it enabled the intercorrelation of the relative configurations of the individual sugars.

A 100 years ago the purification and unequivocal identification of a compound was a formidable task, requiring crystallinity of the compound as well as a preferably sharp melting point and a constant optical rotation. Hexonic acids certainly formed crystalline lactones, but only under special conditions, and since these lactones exhibited mutarotation, their rotational values were not very useful for comparisons. Here for a second time, phenylhydrazine—and as serendipitously as for the formation of the osazones—proved to be a most useful reagent: when heated with an aldonic acid in aqueous acetic acid, the phenylhydrazides of these acids are formed, which crystallize exceedingly well, exhibit sharp melting points and constant rotational values, and thus, were ideal derivatives for the purification and identification of such sugar acids.<sup>[50]</sup>

Accordingly, when Fischer repeated Kiliani’s work on the C<sub>1</sub> extension of the arabinose derived from sugar beet, and—for identification purposes—heated the reaction mixture (allegedly containing only L-mannonic acid) with phenylhydrazine, he obtained not one, but two phenylhydrazides. Both crystallized in the form of prisms, but their melting points were 20 °C apart.<sup>[50]</sup> After a lengthy purification procedure he succeeded in isolating the one with the lower melting point in pure form (Fig. 13), which, upon hydrolysis, proved to be the enantiomer of the acid derived from natural glucose by gentle oxidation. In this way a second complete set of enantiomers, namely D- and L-glucose, became available.<sup>[51]</sup>

As it turned out, this is the first example of an asymmetric synthesis recorded in the literature, on which Fischer commented in the following way:<sup>[52]</sup>

“The simultaneous formation of the two stereoisomeric products on the addition of hydrogen cyanide to alde-

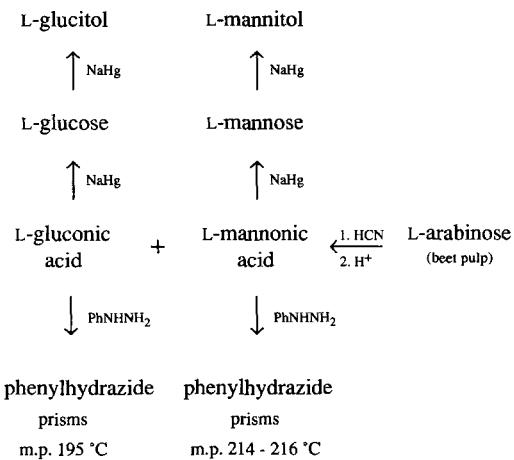


Fig. 13. The first example of an asymmetric synthesis recorded in the literature: not only L-mannonic acid is formed by cyanohydrin synthesis from L-arabinose, but also the 2-epimeric L-gluconic acid, as evidenced by its crystalline phenylhydrazide [51]

hydes, which was observed here for the first time, is quite remarkable in theory as well as in practice.”

This first example of an asymmetric synthesis was soon to be followed by a second case, since sodium amalgam reduction of fructose gave rise to two stereoisomeric products, namely, mannitol and sorbitol.<sup>[53]</sup> Fischer clearly realized the basic importance of this result:

“The reduction of fructose is the second reaction in the sugar group, which generates two stereoisomeric products due to the formation of an asymmetric carbon atom. The same phenomenon will undoubtedly be observed much more frequently in the future, and most probably will be generally found with all compounds that are asymmetric a priori.”<sup>[53]</sup>

Another milestone in the quest for the configurations of sugars proved to be the ensuing chemistry of xylose.<sup>[54]</sup> The discovery of this sugar in cherry gum in 1886<sup>[55]</sup> and the establishment of its pentose structure by Tollens et al. two years later<sup>[56]</sup> came at a most opportune time for Fischer’s work. In 1890 he undertook a study of xylose by applying the cyanohydrin synthesis, which led to a hexonic acid different from any yet encountered.<sup>[57, 58]</sup> It could be reduced to a new sugar and oxidized to a 1,6-dicarboxylic acid, which proved to be the enantiomer of the one obtained from natural glucose. This new sugar was named gulose by Fischer “by exchanging the letter l and u in glucose and eliminating the c”<sup>[58]</sup> Figure 14 summarizes these interrelationships, refraining from the use of chemical formulas—as Fischer did at the time—yet providing the D- and L-assignments later adopted<sup>[38a, b]</sup> for clarity.

The correlation between D-glucose and D-gulose revealed by this set of reactions, and particularly the fact that they become identical—as mirror images—at the stage of their dicarboxylic acids, must have given Fischer the strong indication that the two sugars are head-to-tail enantiomers, that is, that gulose has its aldehyde group where glucose has the hydroxymethyl function, and vice versa. This rationalization was soon confirmed by another set of reactions starting from D-glucose-derived 1,6-dicarboxylic acid (D-glucaric acid), in

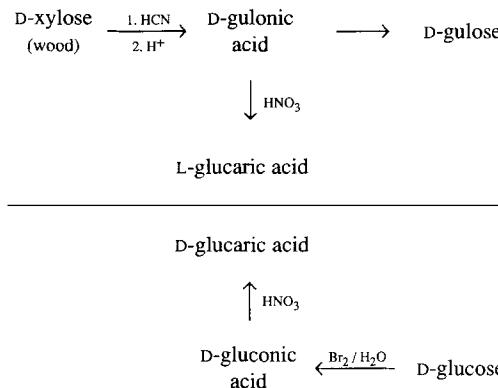
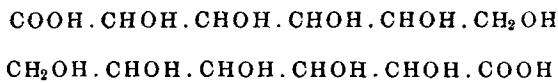


Fig. 14. Experiments which show that D-glucose and D-gulose—on the basis of their 1,6-dicarboxylic acids—are head-to-tail enantiomers. [58, 59].

the form of its 1,4-lactone:<sup>[59]</sup> sodium amalgam reduction first led to D-glucuronic acid, which was identical with the compound isolated from urine 12 years before by Schmiedeberg and Meyer.<sup>[60]</sup> Further reduction generated L-gulonic acid,<sup>[59, 61]</sup> the optical antipode to the hexonic acid obtained from D-xylose by cyanohydrin synthesis.<sup>[62]</sup> In turn, the 1,4-lactone of L-gulonic acid gave L-gulose on treatment with sodium amalgam.<sup>[59]</sup>

The level of comprehension reached by these sets of inter-correlating reactions is clearly evident from a passage of the relevant paper published with Piloty:<sup>[59]</sup>

"A simple consideration shows that gluconic and gulonic acid have the same structure and a very similar configuration. They differ only in the position of the carboxyl group as illustrated by the two formulas,



which are to be viewed stereometrically. Thus, gluconic and gulonic acid are the first examples of stereoisomeric substances which give identical products if the molecule is symmetrical after the conversion of the terminal alcohol groups into carboxyl functions. This observation appears to be an important confirmation of the theory of the asymmetric carbon atom, which predicts 16 isomers for a compound having the structure of gluconic acid; in the case of dibasic acids, their number is reduced to 10. This indicates that one will soon be in a position to determine the configurations of the sugars in terms of the Le Bel–van’t Hoff theory from the factual observations made."

Although the structural formulas given in the citation were to be viewed "stereometrically", half a year prior to his two 1891 landmark papers<sup>[4, 5]</sup> Fischer still avoided the use of configurational representations—an attitude that dramatically changed after unraveling them.

Now, before discussing the actual proof contained in these two publications, a final piece of evidence has to be mentioned which was to have major bearing on uncovering the configurational relationships, namely, the rotational values of the pentose-derived sugar alcohols and 1,5-dicarboxylic acids. The two pentoses known at the time, xylose and ara-

binose, gave the respective pentitols on reduction, neither of which showed any rotation.<sup>[58, 63]</sup> This meant that both are *meso* compounds (Fig. 15). For Fischer, however, this conclusion was too important to be based on the optical inactivity of one compound only, especially since it was known that the alditoles encountered so far had comparatively small rotational values.

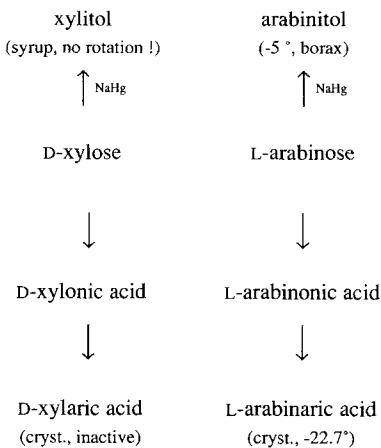


Fig. 15. Correlation between configuration and optical activity of the pentitols and their trihydroxyglutaric acids.

To substantiate this conclusion, Fischer prepared the respective 1,5-dicarboxylic acids by nitric acid oxidation, which each gave crystalline products (Fig. 15). The trihydroxyglutaric acid derived from xylose was indeed optically inactive,<sup>[64]</sup> yet the arabinaric acid showed a distinct negative rotation. Therefore, Fischer again inspected the rotation of the arabinitol; only on addition of borax, that is, with arabinitol in the form of its boric acid complex, was a small negative rotation finally observed,<sup>[58]</sup> thus completing the scheme (Fig. 15).

In this context, we are in the fortunate position to add some personal details to these sober experimental facts. In Fischer's autobiography "Aus meinem Leben"<sup>[19]</sup> there is a delightful passage, which refers to the trihydroxyglutaric acids, and I would like to quote the relevant section:<sup>[65]</sup>

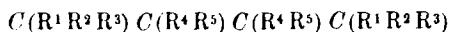
"The Easter Holidays of 1891 I spent at Bordighera on the Italian Riviera in the company of Baeyer. Needless to say, on our extensive walks, and during the meals we took together, we had intense discussions; there was no important problem of chemistry which we would not have covered. I particularly remember one stereochemical question. In the preceding winter of 1890/91 I was occupied with the task of clarifying the configuration of the sugars without completely achieving my goal. In Bordighera the idea occurred to me to make the decision concerning the configuration of the pentoses from their relationships to the trihydroxyglutaric acids. Unfortunately, due to the lack of models I could not determine how many of such acids were theoretically possible, and thus, I put this question to Baeyer. He took up such questions with great warmth and immediately started to construct carbon atom models from toothpicks and little balls of bread. However, after many attempts he finally gave up, allegedly because it



Fig. 16. Jacobus Henricus van't Hoff (1852–1911) around 1889 [6].

became too difficult for him. Later only back in Würzburg, I succeeded in finding the final solution by extensive study of good models."

The solution Fischer succeeded in finding was based on the theory of Le Bel and van't Hoff.<sup>[2, 3]</sup> On the basis of purely theoretical considerations, van't Hoff (Fig. 16) had predicted in 1874 that for the case with four chiral carbon centers 16 isomers can be expected. These 16 isomers of the general formula



were formulated by van't Hoff as depicted in Figure 17, in which the + and – signs allude to the sign of rotation of the individual chiral centers.

				11	12	13	14	15	16
+	+	-	-	+	+	+	+	+	-
+	-	+	-	+	-	-	-	-	+
+	-	+	-	-	+	-	-	-	-
+	+	-	-	-	+	-	-	-	-
1	2	3	4	+	-	-	+	-	-
				+	+	+	-	-	+
				+	+	+	+	+	-
				5	6	7	8	9	10

Fig. 17. Van't Hoff's prediction of configurational isomers for compounds with four chiral carbon centers, in his + and – notation [3].

Accordingly, the isomers 1 and 4 are enantiomers, as are the isomers 2 and 3; the other twelve possibilities are listed in such a way as to illustrate the head-to-tail mirror-image symmetry: isomer 5 is the enantiomer of 11, this relationship is also valid for 6 and 12, 7 and 13 etc. In the case where both ends have identical substituents, as in the hexitols and 1,6-dicarboxylic acids, the isomers 5–10 become identical with 11–16, so the total number of isomers then would be reduced to 10.

The task with which Fischer had been occupied in the years preceding 1891 was a formidable one: to select the

configuration from the sixteen possibilities that represent grape sugar, on the basis of the experimental evidence that had been accumulated. This required models. Those van't Hoff used for his theoretical deductions are shown in Figure 18. Fischer must have used these too, since van't Hoff<sup>[3]</sup> gave detailed instructions on how to prepare them from cardboard in an appendix to his brochure.

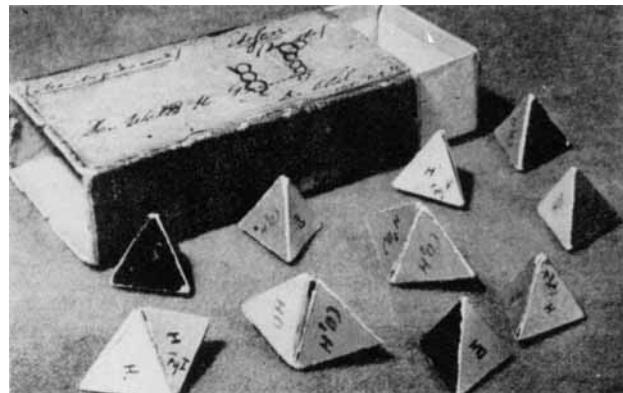


Fig. 18. "Match box" models of van't Hoff (preserved in the chemistry museum of the Maison de la Chimie of the French Chemical Society, Paris).

In his second landmark paper of 1891,<sup>[5]</sup> however, Fischer also referred to the use of "Friedländer rubber models", the essentials of which were described by V. Meyer:<sup>[66]</sup>

"They consist of four short pieces of rubber tubing, whose inner diameter is approximately the thickness of a match, and which are soldered together in the middle, so that they extend into space in a tetrahedral arrangement."

These models appear to be very close to the ball and stick models, or those of the Fieser or Dreiding type in use today. Evidently as a result of his extensive use of models, and his intense intellectual involvement in correlating the experimental data available with the 16 sugar configurations available, Fischer arrived at the solution laid down in his first 1891 paper: grape sugar, the natural glucose, has the – + + + configuration (Fig. 19), D-mannose has the + + + + configuration, and D-fructose with only three asymmetric centers, correspondingly, + + +.<sup>[4]</sup>

Now, rather than presenting the Fischer proof of the sugar configuration in the terms of the van't Hoff notation, it is more appropriate and expedient to proceed here as Fischer did: within two months of proposing the sugar configurations in the +/– terminology, he discarded this system altogether, and replaced it by his own. There was ample reason for that. The + and – signs used by van't Hoff for designating the configurations at asymmetric carbon atoms are very confusing, because they are derived by observing the individual tetrahedra—as arrayed in a model (Fig. 20)—from a point within the model, namely, its center. This refers to the center of the whole molecule and not that of an individual tetrahedron. For tartaric acid, the center of the molecule is clear: its the apex where the two tetrahedra are joined (marked by an asterisk in Figure 20); on looking up from that point of reference, the sequence of OH → H is perceived to be counterclockwise, so the asymmetric carbon atom receives a – sign, whereas looking down from the apex results

**Aldosen:** COH . CH(OH) . CH(OH) . CH(OH) . CH(OH) . CH<sub>2</sub>OH

d. Glucose	-	+	+	+
l. Glucose	+	-	-	-
d. Mannose	+	+	+	+
l. Mannose	-	-	-	-

**Ketosen:** CH<sub>2</sub>OH . CO . CH(OH) . CH(OH) . CH(OH) . CH<sub>2</sub>OH

d. Fructose	+	+	+
l. Fructose	-	-	-

**Alkohole:** CH<sub>2</sub>OH . CH(OH) . CH(OH) . CH(OH) . CH(OH) . CH<sub>2</sub>OH

d. Sorbit	-	+	+	+
l. Sorbit	+	-	-	-
d. Mannit	+	+	+	+
l. Mannit	-	-	-	-

#### Zweibasische Säuren:

COOH . CH(OH) . CH(OH) . CH(OH) . CH(OH) . COOH.

d. Zuckersäure	-	+	+	+
l. Zuckersäure	+	-	-	-
d. Mannozuckersäure	+	+	+	+
l. Mannozuckersäure	-	-	-	-

Fig. 19. Fischer's configurational assignments to glucose, mannose, and fructose in the van't Hoff notation [4].

in a clockwise order of OH towards H, and it is given a + sign. The signs compensate each other, as would do the individual rotational contributions of the two carbon atoms, hence they denote the *meso* form of tartaric acid.

The situation becomes more difficult in cases with three chiral centers, since the "center" of the molecule has to be defined. For pentoses this was placed at the apex between the first and second asymmetric carbon (see position of the asterisk in Fig. 20, center), which results in a + + + sequence of signs for D-arabinose. In hexoses, the point of reference is again the center of the molecule, (Fig. 20 right) which results in the - + + + sequence for D-glucose.

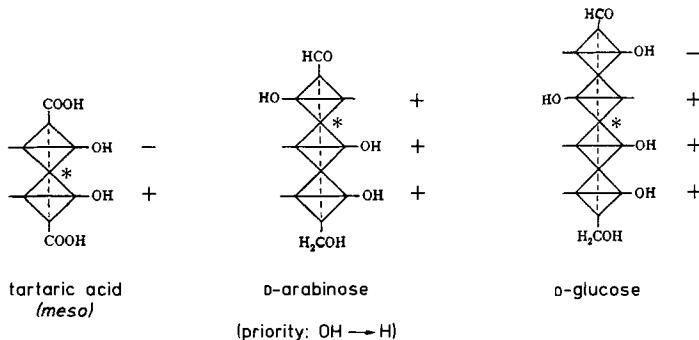


Fig. 20. Derivation of van't Hoff's + and - signs from the "center" (marked by \*) of the respective molecules.

Fischer soon realized<sup>[5]</sup> that "the designation of spacial relationships by + and -, which were introduced by van't Hoff and which were retained by me in unchanged form, can easily lead to an erroneous view in the case of such complicated molecules. To prevent this, I consider a more detailed interpretation of the formula an urgent necessity."

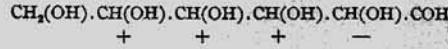
Thus, within two months after the submission of the first 1891 paper (received at Berichte on June 6<sup>[4]</sup>) Fischer dispatched a second one (received: August 8<sup>[5]</sup> (Fig. 21) in which he replaced the + and - system of van't Hoff by his

#### 48. Emil Fischer: Über die Konfiguration des Traubenzuckers und seiner Isomeren. II.

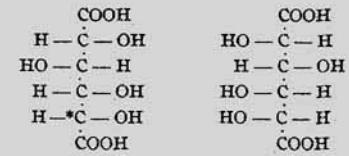
[Aus dem chemischen Laboratorium der Universität Würzburg.]

(Eingegangen am 8. August.)

In der ersten Abhandlung<sup>1)</sup> habe ich für den Traubenzucker die Formel



entwickelt. Die Bezeichnung der räumlichen Anordnung durch + und -, welche von van't Hoff eingeführt und von mir in unveränderter Form beibehalten wurde, kann aber bei solchen komplizierten Molekülen leicht eine irrtümliche Auffassung zur Folge haben. Um dies zu verhüten, halte ich eine ausführlichere Interpretation der Formeln für nötig.



Ich wähle wieder willkürlich für die d-Zuckersäure die Form I, wobei es natürlich unentschieden bleibt, ob bei dem mit \* bezeichneten Kohlenstoffatom die Reihenfolge von Hydroxyl und Wasserstoff im Sinne des Uhrzeigers oder umgekehrt statthat. Dann ergeben sich für Traubenzucker und seine Isomeren folgende Formen:

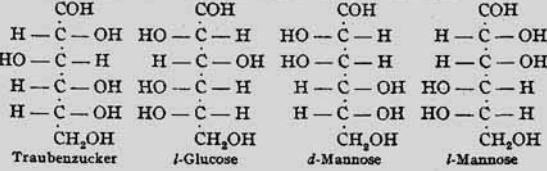


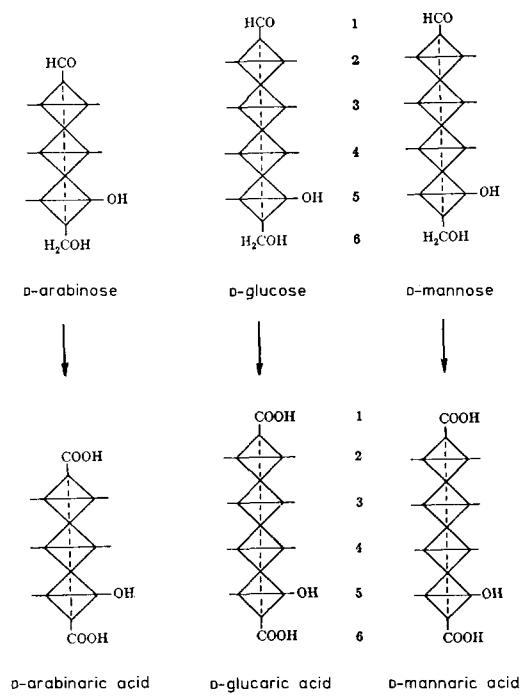
Fig. 21. The second of Fischer's 1891 landmark papers on the configurations of the sugars, with which he introduced the Fischer mode of writing stereoformulas [5].

own: representation of tetrahedral space relationships by their projection into a plane. The resulting formulas were simple to write and easy to visualize, yet required the setting up of conventions; the ones he chose seem as few in number and as simple in character as possible: The carbon chain of a sugar is oriented vertically and to the rear with the aldehyde group at the top; the hydrogen atoms and hydroxyl groups at the asymmetric carbon atoms stand out in front. The resulting three-dimensional model is then imagined to be flattened and the groups are laid on the plane of the paper. If the lowermost asymmetric center (i.e., C-5 in glucose) has the OH group to the right, it is considered to have the D-configuration. Fischer's decision to place the OH group of natural glucose to the right, hence D-glucose, was purely arbitrary, yet proved to be a fortunate one, since much later in 1951, it was proved by special X-ray structural techniques<sup>[6,7]</sup> that he had made the right choice.

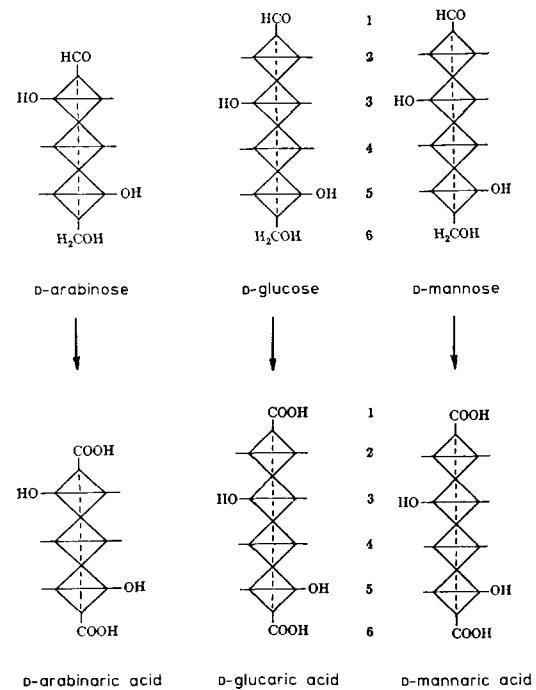
The change of the + and - notation to the projection mode of writing stereoformulas is strikingly evident in the second 1891 paper,<sup>[5]</sup> (Fig. 21) and this was soon universally adopted. In this presentational mode, by using Fischer's convention that the asymmetric carbon atoms (tetrahedra) have the lower edge in the plane of the paper whilst the corners carrying the H and OH groups lie above this plane can now be delineated.<sup>[6,8]</sup>

1. Since glucose was selected by definition as having the OH group at the lowermost asymmetric carbon atom at the

right, all chemically interrelated compounds are of D-configuration:

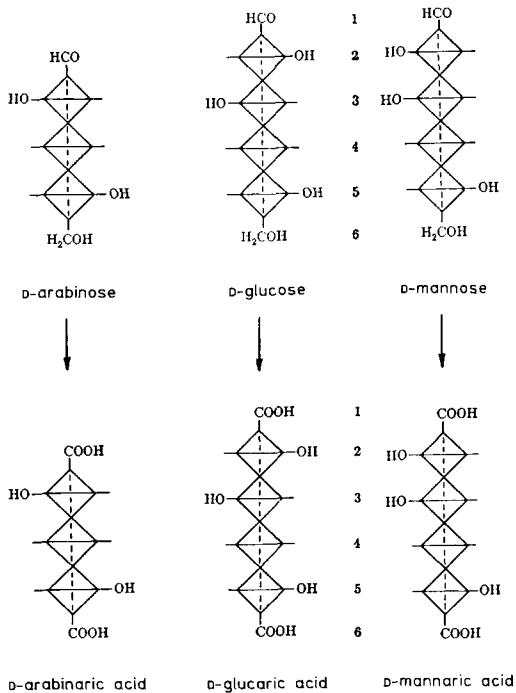


2. The D-arabinic acid showed a distinct optical rotation, thus cannot be a *meso* compound. This means that the OH group at C-2 of D-arabinic acid must be to the left and thus determines the relative configuration at C-3 of the two hexoses. Therefore, in the entire set of compounds depicted here the OH group is to be placed to the left:

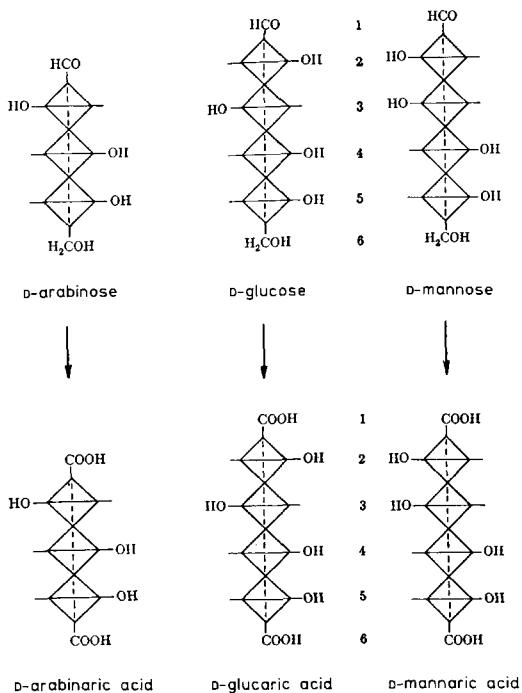


3. D-Glucose and D-mannose are C-2 epimers; hence their 2-hydroxyl groups are oriented in opposite directions. Either one may be selected as having the OH on the right; in

the following Figure D-glucose is—for now—arbitrarily considered to have the C-2 OH group to the right, and consequently this group is oriented to the left in D-mannose:

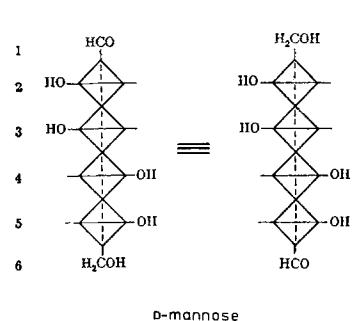
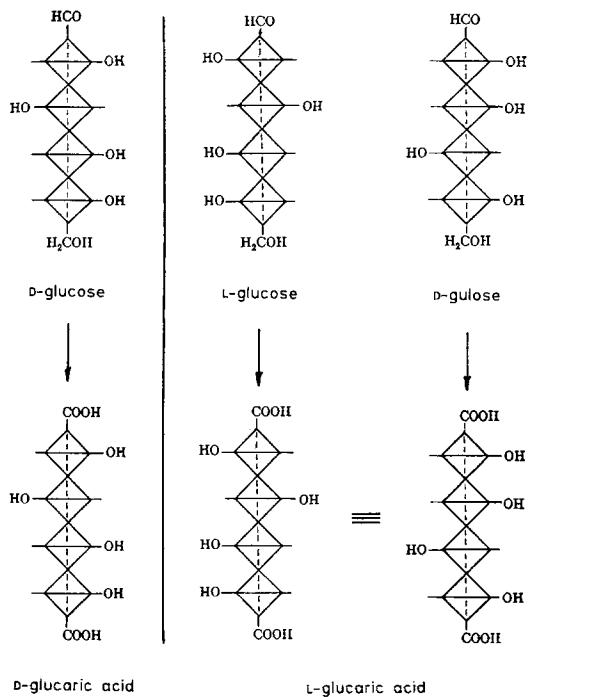


4. Since both D-glucaric and D-mannaric acids are optically active, the configuration of neither of them can possess end-to-end symmetry; hence the OH group on C-4 must be on the right (if it were on the left, the glucaric acid would have end-to-end symmetry and, hence be optically inactive). At this stage the configuration of D-arabinose and its dicarboxylic acid have been established:



5. D-Glucose and D-mannose have been limited to two configurations but final specification remains to be established. This was done on the basis of the following reason-

ing: D-glucaric acid is obtained from the oxidation of D-glucose, the enantiomeric L-glucaric acid analogously from L-glucose, but also from D-gulose. This is only possible, if D-gulose is the head-to-tail configurational isomer to L-glucose:



D-Gulose, upon exchange of its aldehyde group with CH<sub>2</sub>OH and vice versa, yields a different aldose, namely, L-glucose. Applying the same operation to D-mannose, the product is again D-mannose, thus providing a further substantiation of conclusions 1-5:

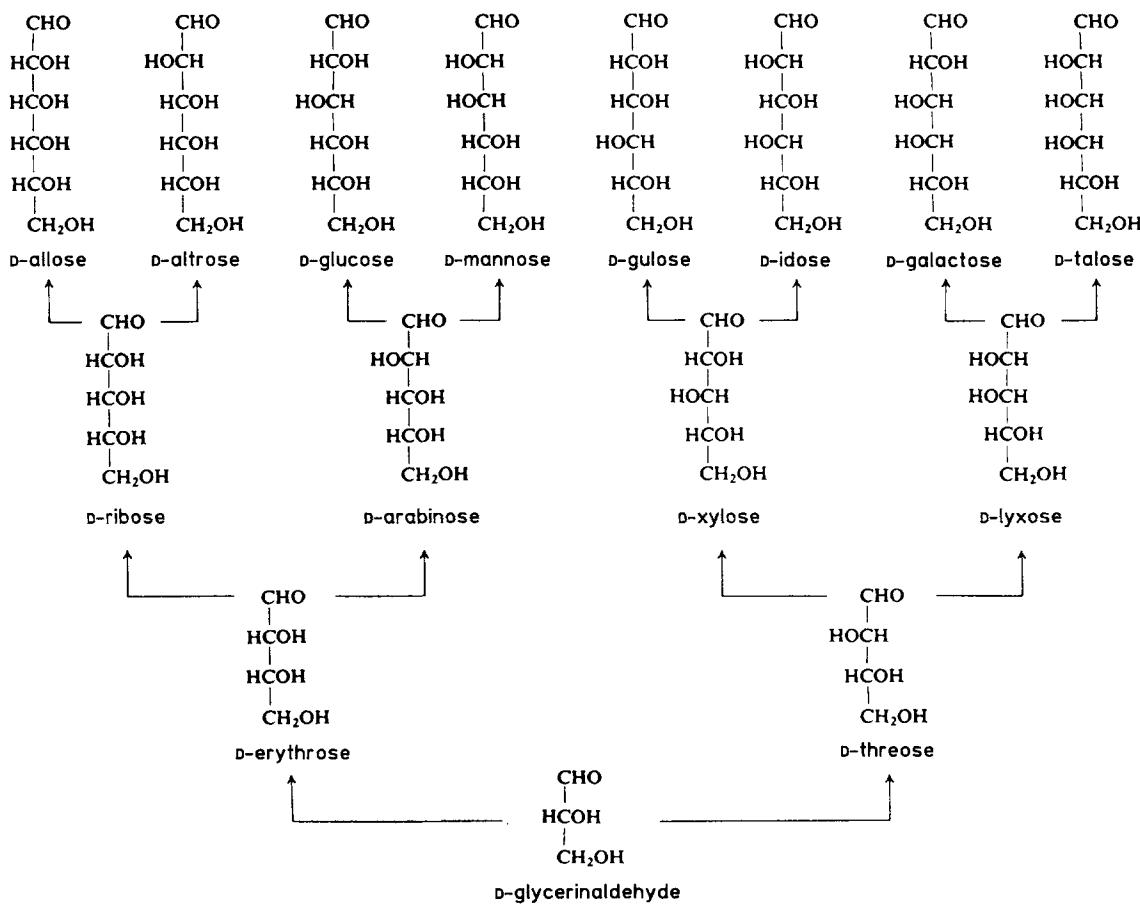


Fig. 22. The sugar family tree of D-aldoses.

fronted with the paradox that at this stage the development of chemistry did not proceed from the understanding of simple cases to the gradual comprehension of more complex ones, but vice versa.

In this context, a number of contemporaries had all the knowledge at hand to unravel the sugar configurations—Kiliani,<sup>[69]</sup> for example, and Tollens, who later was to write the first comprehensive treatise on carbohydrate chemistry<sup>[70]</sup>—but it was Emil Fischer who, endowed with a brilliant mind and the necessary self-confidence and perseverance, attacked the problem systematically and after only seven years of involvement with the chemistry of the sugars found the solution.

This classical piece of work was not to remain the only great service Fischer rendered to chemistry, since later he returned to the work he had started in 1882 in Munich on purines. This led to the classification of this class of substances<sup>[71]</sup> and subsequently to the synthesis of the first nucleosides.<sup>[72]</sup> Around the turn of the century Fischer began his third great series of investigations on amino acids, polypeptides, and proteins and laid the chemical and biochemical foundations for this field.<sup>[13]</sup> Finally in 1908 he began work on a further class of natural products, the tannins.<sup>[74]</sup> The brilliant synthetic work in the sugar series, however, and the manner in which he applied and developed the van't Hoff–Le Bel theory for elucidating their stereochemistry

stands out—in my opinion—as the pinnacle of his scientific career.

Not only we today, a century later, marvel at this classic example of exact mathematical reasoning in an experimental science, and at the man who accomplished it; his contemporaries also recognized his genius by bestowing many honors on Fischer of which two are mentioned here: in 1892 at the age of 40, mostly on the basis of his work on the sugars, Fischer was offered the most coveted chair of chemistry at the time, at the University of Berlin (Fig. 23), to become successor to A. W. von Hofmann (1818–1892), and in 1902 he was awarded the Nobel Prize in chemistry, the second one ever to be awarded; notably, the recipient of the first in 1901 was van't Hoff. The president of the Royal Swedish Academy of Sciences put his appreciation into the following words:<sup>[75]</sup>

"The specific type of research which has characterized organic chemistry during the final decades of the nineteenth century, attained its zenith of development and its finest form in Fischer's studies of sugars and purines. From the experimental point of view they are unsurpassed."

In concluding this centennial tribute to one of the really great figures of our science, a passage from his 1890 lecture at the University of Berlin, in which he outlined the strategy he followed in the pursuit of the sugar configurations, may give a final glimpse of the spirit of the man in his quest for knowledge:<sup>[76]</sup>

"I would like to compare chemical investigations of this sort which become more difficult with every step, with the construction of a tunnel. If a mountain ridge is not too wide, one succeeds in driving the tunnel through in one direction. Otherwise, the engineer is forced to start work from the opposite site. However, he is in the fortunate position of being able to predetermine the site of the attack by exact measurements and, thus, is assured of joining the tracks inside.

Our science, unfortunately, is as yet not deductive enough to allow such calculations. The chemist may consider himself fortunate if he drives his tunnels through matter from opposite sites and finds the connection inside, albeit after several zigzag moves. Such a piece of good luck led me to the target."

This should remind us that hard experimental work, clear evaluation of results, mathematical reasoning, and a superb strategy is not all. A piece of serendipity is also involved in the solution of the fundamental problems of science.

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German version: *Angew. Chem.* **1992**, *104*, 1577



Fig. 23. Emil Fischer around the turn of the century in his laboratory at the University of Berlin [18].

[1] A. Kekulé, *Bull Soc. Chim. Fr.* **1865**, *3*, 98; *Justus Liebigs Ann. Chem.* **1866**, *137*, 129; K. Hafner, *Angew. Chem.* **1979**, *81*, 685; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 641.

[2] J. A. Le Bel, *Bull. Soc. Chim. Fr.* **1874**, *22*, 337.

[3] J. H. van't Hoff, *Die Lagerung der Atome im Raume*, Vieweg, Braunschweig, 1877. This, at the time widely distributed, 53-page booklet is the thoroughly revised German version of van't Hoff's brochure *La chimie dans l'espace* (Bazendijk, Rotterdam, 1875), which, in turn, is a French translation (by van't Hoff himself) of the original Dutch text *Voorstel tot uitbreidiging in de scheikunde gebruikte structuurformules in*

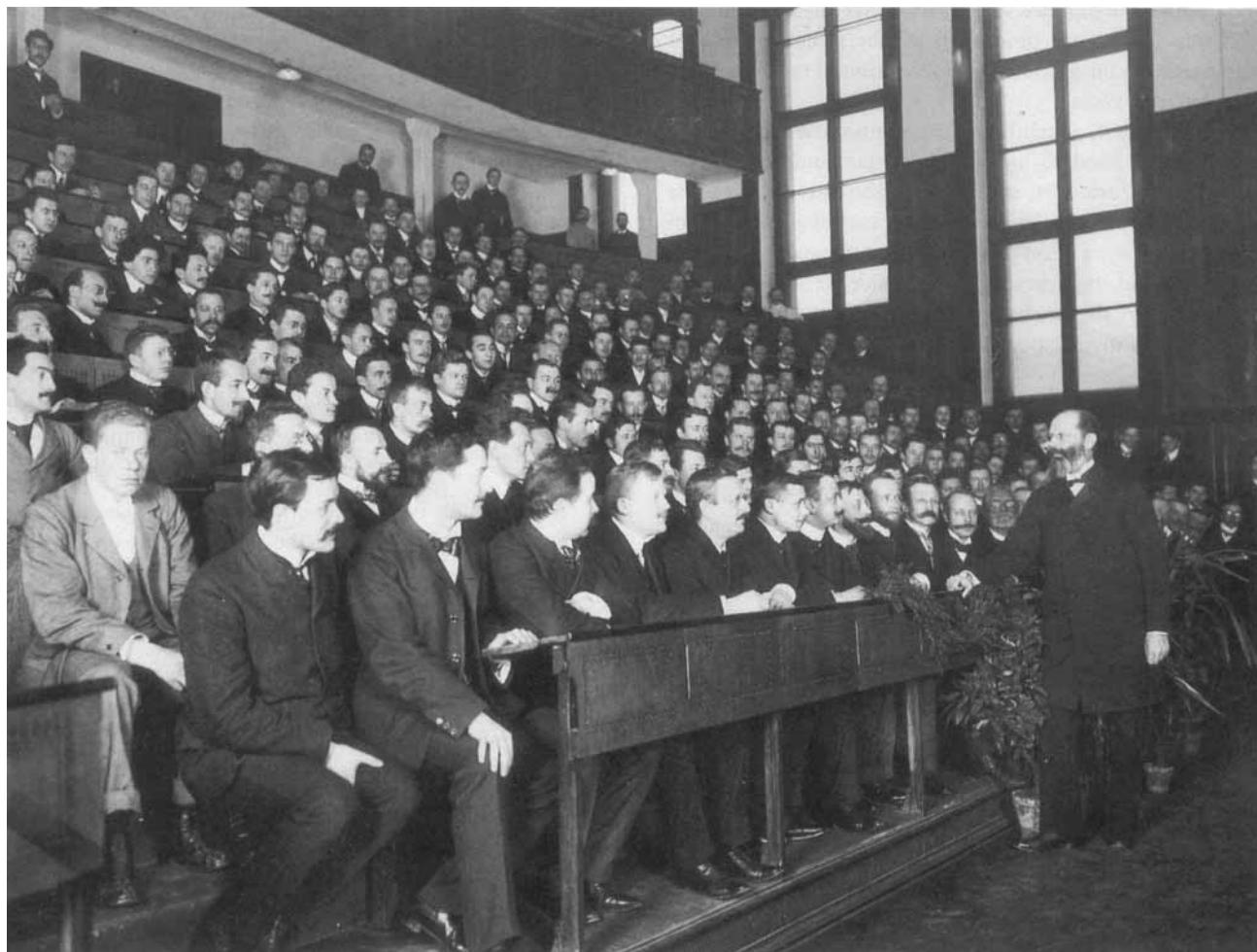


Fig. 24. Festive Colloquium on December 16, 1902 in the Fischer Lecture Hall of the Chemical Institute of the University of Berlin, in honor of Emil Fischer having received the Nobel Prize in Chemistry the week before [18].

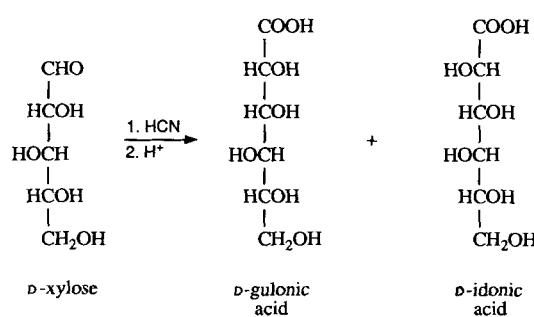
*de rechte* (Greven, Utrecht, 1874). The translation into German was done by F. Herrmann instigated by J. Wislicenus, who contributed a most favorable preface, in which he stood up against "the multifold, obstinate misunderstanding of the ideas" (of van't Hoff), by appraising them as "a real and important step forward". E. Fischer used this 1877 German version for his stereochemical deductions referring to it as "Broschüre von van't Hoff-Herrmann".

- [4] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1891**, 24, 1836.
- [5] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1891**, 24, 2683.
- [6] Picture from the congratulatory album of photographs presented to August von Kekulé on the occasion of his 60th birthday (September 6, 1889). The original document is in the collection of Kekulé papers, in the Institut für Organische Chemie, Technische Hochschule Darmstadt.
- [7] L. Knorr, "Über die wissenschaftlichen Arbeiten und die Persönlichkeit Emil Fischers", *Ber. Dtsch. Chem. Ges.* **1919**, 52, 132–149.
- [8] C. Harries, "Emil Fischer's wissenschaftliche Arbeiten", *Naturwissenschaften* **1919**, 7, 843–860.
- [9] M. O. Forster, "Emil Fischer Memorial Lecture", *Trans. Chem. Soc. (London)* **1920**, 117, 1157–1201.
- [10] K. Hoesch, "Emil Fischer, sein Leben und sein Werk", *Ber. Dtsch. Chem. Ges.* (special issue) **1921**, 54; also issued as a book with the same title, Verlag Chemie, Berlin/Leipzig (1922). This biography, written in an overly pathetic, pompous style appears to have been well perceived by many of Fischer's contemporaries, as evidenced by enthusiastic letters of approval from C. Duisberg, A. Gabriel, C. Neuberg and H. Pringsheim [10a]. However, it also met strong criticism; C. Harries who over years had been the assistant in the experimental lecture courses given by A. W. von Hofmann and from 1892 on by E. Fischer, happened to be president of the Deutsche Chemische Gesellschaft, which had commissioned the biography. He strongly disapproved of the fact that he was deprived of seeing the manuscript before publication, and added [10b]: "It is a poetic achievement, a well-accomplished dithyramb on the adored teacher. Unfortunate-

ly, however, the author has got carried away by his temperament and made statements that transgress the poetically allowed, which for historical reasons cannot remain uncontradicted. What primarily has to be objected is the comparison of A. W. von Hofmann, Adolf von Baeyer, and Viktor Meyer with Emil Fischer. It is certainly permitted to make comparative evaluations of illustrious personalities, however, a protest must be made about the form, in which this was done here. Quite bluntly the intended portrayal of Emil Fischer unconditionally as the greatest is obvious. A. W. von Hofmann and Viktor Meyer come off quite badly. Instead, we should be delighted that we had such a series of great men, and hence should not attempt to exalt one to be the most important, since each of them more or less stood on the shoulders of the others." R. Willstätter [10c] also criticizes Hoesch's presentation for lack of depth, insufficient inside knowledge, and its "pathetic style", in sharp contrast with Fischer's refreshing informality. H. O. L. Fischer (1888–1960 [10d]), Emil Fischer's son, initially (1922) approved of the biography: "I am delighted that you have solved your task in a literally splendid, comprehensive, and sympathetic, warm-hearted form" [10a]; in later years (1959), however, he had arrived at a distinctly different opinion: "The Hoesch biography of my father is essentially unreadable, even by an educated German" [10e]. a) The relevant letters to K. Hoesch, dating from 1922 and 1923, are in the Emil Fischer Collection in the Bancroft Library, University of California, Berkeley, the citations given with their kind permission. b) Presentation at a meeting of the Deutsche Chemische Gesellschaft in Berlin on July 3, 1923; the manuscript is in possession of the Bancroft Library. c) R. Willstätter. *Aus meinem Leben*, 3rd edition, VCH, Weinheim, 1979, p. 212. An English translation was prepared by L. S. Hornig, Benjamin, New York, 1965. d) H. O. L. Fischer, "Fifty Years in the Service of Biochemistry", *Annu. Rev. Biochem.* **1960**, 29, 1–14; F. W. Lichtenthaler, *Carbohydr. Res.* **1987**, 156, 1–22. e) Personal communication to C. E. Ballou and the author.

- [11] C. S. Hudson, "Emil Fischer's Discovery of the Configuration of Glucose", *J. Chem. Educ.* **1941**, 18, 353–357.

- [12] C. S. Hudson, "Historical Aspects of Emil Fischer's Fundamental Conventions for Writing Stereoformulas in a Plane", *Adv. Carbohydr. Chem.* **1948**, 3, 1–22.
- [13] K. Freudenberg, "Emil Fischer and His Contribution to Carbohydrate Chemistry", *Adv. Carbohydr. Chem.* **1966**, 21, 1–38.
- [14] J. S. Fruton, *Contrasts in Scientific Style. Research Groups in the Chemical and Biochemical Sciences*, Am. Phil. Soc., Philadelphia, **1990**, pp. 163–229 and 375–403.
- [15] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1875**, 8, 589; G. B. Kauffmann, R. P. Ciula, *J. Chem. Educ.* **1977**, 54, 295.
- [16] T. Curtius, *Ber. Dtsch. Chem. Ges.* **1887**, 20, 1632.
- [17] R. Huisgen, *Angew. Chem.* **1986**, 98, 297; *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 303.
- [18] The original and numerous other photographs are contained in the Collection of Emil Fischer Papers, housed in the Bancroft Library at the University of California, Berkeley. This scientific bequest consists of 34 boxes of material: lab notes, manuscripts, drafts of his autobiography "Aus meinem Leben", which differ from the published version [19], and about 5000 letters, mostly handwritten, that reached Fischer during his 40-year scientific career; for example, 157 letters during 1889–1915 from his teacher A. von Baeyer, others from F. Beilstein (11), A. Hantsch (56), F. Haber (35), J. H. van't Hoff (31), A. W. Hofmann (5), A. von Kekulé (6), H. Kiliani (16), V. Meyer (46), W. Nernst (67), B. Tollens (20), P. Walden (13), O. Wallach (46), and R. Willstätter (33); Fischer's intense interaction with industry is documented by 181 letters from C. Duisberg (from 1895–1919), from Bayer (271), BASF (54), Boehringer Mannheim (116), Hoechst (50) and Merck (33). Surprisingly, the collection contains also two letters from Konrad Adenauer, written in 1918 as Lord Mayor of Cologne, concerning the establishment of a Kaiser-Wilhelm Institute for Physiology. The papers eventually reached Berkeley through Fischer's son, Hermann Otto Laurens Fischer, [10d] who carried this collection along with him through all the stations of his unusually cosmopolitan career: Privatdozent in Berlin, Professor of Pharmaceutical Chemistry in Basel, Director of the Banting Institute, Toronto, and Professor of Biochemistry at the University of California, Berkeley. The papers were donated to the Bancroft Library by Mrs. H. O. L. Fischer in November 1970.
- [19] E. Fischer, *Aus meinem Leben*, Springer, Berlin, **1987**, (reprint of the original 1922 version with an English commentary by B. Witkop).
- [20] E. Fischer, O. Fischer, *Ber. Dtsch. Chem. Ges.* **1876**, 9, 891; *Justus Liebigs Ann. Chem.* **1878**, 194, 242; *Ber. Dtsch. Chem. Ges.* **1880**, 13, 2204.
- [21] T. Curtius, J. Bredt, "Wilhelm Koenigs", *Ber. Dtsch. Chem. Ges.* **1912**, 45, 3787–3830.
- [22] W. Koenigs, E. Knorr, *Sitzungsber. Bayr. Akad. Wiss.* **1900**, 30, 108; *Ber. Dtsch. Chem. Ges.* **1901**, 34, 957.
- [23] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1876**, 9, 880; *Justus Liebigs Ann. Chem.* **1878**, 190, 134.
- [24] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1884**, 17, 579.
- [25] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1881**, 14, 637, 1905; *ibid.* **1882**, 15, 29, 453; *Justus Liebigs Ann. Chem.* **1882**, 215, 253.
- [26] E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, 16, 2241; E. Fischer, O. Hess, *ibid.* **1884**, 17, 559; E. Fischer, *Justus Liebigs Ann. Chem.* **1886**, 236, 116.
- [27] P. A. Roussel, *J. Chem. Educ.* **1953**, 30, 122; B. Robinson, *Chem. Rev.* **1963**, 63, 373.
- [28] A. Baeyer, *Ber. Dtsch. Chem. Ges.* **1870**, 3, 67.
- [29] H. Schiff, *Ann. Chem. Pharm.* **1870**, 154, 344.
- [30] R. Fittig, *Über die Constitution der sogenannten Kohlenhydrate*, L. F. Fues, Tübingen, **1871**. This 35-page treatise was attached to the invitation for the academic celebration of the birthday of his Majesty, King Karl of Württemberg, on March 6, 1871 and, due to its low circulation, responsible for the oversight of Fittig's contribution by most of his contemporaries. A copy is in the possession of the Hessische Landesbibliothek, Darmstadt, evidently due to the fact that the Grandduke of Hesse, who resided in Darmstadt, received such an invitation.
- [31] B. Tollens, *Ber. Dtsch. Chem. Ges.* **1883**, 16, 923.
- [32] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1887**, 20, 821.
- [33] E. Fischer, J. Hirschberger, *Ber. Dtsch. Chem. Ges.* **1888**, 21, 1805.
- [34] E. Fischer, J. Hirschberger, *Ber. Dtsch. Chem. Ges.* **1889**, 22, 365.
- [35] R. Gans, W. E. Stone, B. Tollens, *Ber. Dtsch. Chem. Ges.* **1888**, 21, 2148; R. Gans, B. Tollens, *Justus Liebigs Ann. Chem.* **1888**, 249, 256.
- [36] R. Reiss, *Ber. Dtsch. Chem. Ges.* **1889**, 22, 609.
- [37] E. Fischer, J. Hirschberger, *Ber. Dtsch. Chem. Ges.* **1889**, 22, 3218.
- [38] In Figures 10–15 the gradually evolving affiliation of the individual sugars and their derivatives to the D- or L-series has already been made. It should be noted though, that Fischer only introduced the symbols d and l late as 1890 [38a], deriving their meaning from the sign of rotation: "Since sugar derivations change their sign of rotation from right to left and vice versa, I propose to designate all compounds of a series according to the sign of rotation of the aldehyde with the letters d (dextro) or l (levo), just like the letters o, m and p are used in the case of benzene derivatives". [38] Only later did Fischer take this a step further, so that the signs d and l were not uniformly derived from the sign of rotation of the parent sugar, but they were also used to express similar or identical steric arrangements between related compounds. "Thus, I designated natural fructose, which features the same configuration as d-glucose, the d-designation despite its levorotation [38b]." Rosanoff in 1906 [38c], and Wohl and Freudenberg in 1923 [38d] brought the use of the d and l symbols on a logical, genetic basis by selecting the enantiomeric glyceraldehydes as points of reference, such that any sugar belongs to the d-series, if it can be derived from d-glyceraldehyde by successive Kiliani–Fischer syntheses. For sugars defined in this way Rosanoff originally proposed to use δ- and λ-symbols, which did not gain general acceptance. The present use of the d- and l-notation [38e] started around 1940 [38f]. a) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 370; b) *ibid.* **1907**, 40, 102; c) M. A. Rosanoff, *J. Am. Chem. Soc.* **1906**, 28, 114; d) A. Wohl, K. Freudenberg, *Ber. Dtsch. Chem. Ges.* **1923**, 56, 309; e) Rules of Carbohydrate Nomenclature, No. 4 and 5, in *The Carbohydrates, Vol. II B* (Eds.: W. Pigman, D. Horton), Acad. Press, New York, **1970**, p. 809 ff; f) In the monographs of F. Michel (*Chemie der Zucker und Polysaccharide*, 1st Edition, Akad. Verlagsges., Leipzig, **1939**) and H. Elsner (*Grundriß der Kohlenhydratchemie*, Verlag Parey, Berlin, **1941**) the d and l symbols are still used exclusively.
- [39] The Emil Fischer Collection in the Bancroft Library [18] not only contains the original letters (157) written by Baeyer to Fischer, but also carbon copies of those written by Fischer to his mentor.
- [40] W. Hückel, "Heinrich Kiliani", *Chem. Ber.* **1949**, 82, I–IX.
- [41] H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1885**, 18, 3066; *ibid.* **1886**, 19, 221.
- [42] H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1886**, 19, 3029; *ibid.* **1887**, 20, 282, 339.
- [43] H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1886**, 19, 767, 1128.
- [44] H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1888**, 21, 915; *ibid.* **1889**, 22, 521.
- [45] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 370.
- [46] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 2114; quotation from p. 2123.
- [47] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1889**, 22, 2204; *ibid.* **1890**, 23, 930.
- [48] E. Fischer, F. Passmore, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 2226.
- [49] E. Fischer, *Justus Liebigs Ann. Chem.* **1892**, 270, 64; *ibid.* **1895**, 288, 139.
- [50] E. Fischer, F. Passmore, *Ber. Dtsch. Chem. Ges.* **1889**, 22, 2728.
- [51] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 2611.
- [52] See [46], p. 2134.
- [53] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 3684.
- [54] a) The naturally occurring levorotatory xylose, that is, D-xylose in today's nomenclature, was originally designated as L-xylose by Fischer [58]. Correspondingly, the products resulting from cyanohydrin synthesis, hydrolysis, and reduction were denoted L-gulonic acid and L-gulose [58]; in the scheme of Figure 14, the D-notation has been applied to these alleged L-compounds, as they are all derived from D-glyceraldehyde. This has to be taken into consideration when studying the older literature [54b, 58]. b) E. Fischer, I. W. Fay, *Ber. Dtsch. Chem. Ges.* **1895**, 28, 1975; E. Fischer, O. Ruff, *ibid.* **1900**, 33, 2142.
- [55] F. Koch, *Pharm. Z. Russl.* **1886**, 25, 619, 635, 651, 747, 763; *Ber. Dtsch. Chem. Ges.* **1887**, 20, 145.
- [56] H. J. Wheeler, B. Tollens, *Justus Liebigs Ann. Chem.* **1889**, 254, 304.
- [57] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 2625.
- [58] E. Fischer, R. Stahel, *Ber. Dtsch. Chem. Ges.* **1891**, 24, 528.
- [59] E. Fischer, O. Piloto, *Ber. Dtsch. Chem. Ges.* **1891**, 24, 521.
- [60] O. Schmiedeberg, H. Meyer, Z. Physiol. Chem. **1879**, 3, 422.
- [61] H. Thierfelder, Z. Physiol. Chem. **1891**, 15, 71.
- [62] "Encumbered" with the present-day knowledge on the reactions outlined in Figure 14, one can't refrain from marveling at the series of fortuitous circumstances which led Fischer to these rather sparse experimental results. For example, the fact that cyanohydrin synthesis of D-xylose, on subsequent hydrolysis, yields a mixture of D-gulonic acid and its C-2 epimer D-idonic acid (E. Fischer, I. W. Fay, *Ber. Dtsch. Chem. Ges.* **1895**, 28, 1975), from which the former could only be isolated because its 1,4-lactone crystallizes outstandingly well: "The gulonic acid lactone belongs to the most beautiful compounds of the sugar group. By slow evaporation of its aqueous solution one easily obtains magnificently formed crystals of 1 cm in diameter" [58].



On the other hand, D-glucaric acid forms two monolactones, and only the lactonized carboxyl function is reduced by sodium amalgam to the aldehyde and subsequently to the primary alcohol. Undoubtedly a case of

serendipity, that "the sugar acid liberated from its cadmium salt by hydrogen sulfide, on concentration to a syrup and subsequent heating on a water bath for 5–6 hours" [59], mainly contained the 1,4-lactone of D-glucaric acid, which gave L-gluconic acid on reduction, isolated as its superbly crystalline 1,4-lactone in 10% yield [59]. If Fischer and Piloy had made efforts to purify the syrup "Zuckerlactonsäure" as obtained above, they would have acquired the crystalline 3,6-lactone, (H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1925**, 58, 2344). On reduction this would have yielded D-glu-

ic acid; of no value in unraveling the interrelationships of the sugars. The formulas are presented as Fischer projections, since present day graphic presentations are not necessarily more appropriate for such configurational comparisons.

- [63] H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1887**, 20, 1234.
- [64] See [58], p. 538.
- [65] See [19], p. 133 and 134.
- [66] V. Meyer, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 572.
- [67] A. F. Peerdemann, A. J. van Bommel, J. M. Bijvoet, *Nature* **1951**, 168, 271; J. Trommel, J. M. Bijvoet, *Acta Crystallogr.* **1954**, 7, 703; J. M. Bijvoet, *Endeavour* **1955**, 14, 71.
- [68] The individual progressive steps of the proof given here try to trace and follow Fischer's chain of reasoning that undoubtedly developed from the van't Hoff thought patterns. For that reason the projection formulas used are provided with the corresponding tetrahedra, from which they are thought to emerge. A similar presentational mode was used by C. S. Hudson in 1941 [11]. It is rare that one finds a textbook of today, which follows the steps of the original proof. A notable exception is *Organic Chemistry* by R. T. Morrison and R. N. Boyd (2nd ed, Allyn and Bacon, Boston, 1970, p. 993–997) which gives a detailed, impressively clear derivation of the sugar configurations in slightly modernized form.
- [69] In his obituary for H. Kiliani, W. Hückel comments on this as follows: [40] "Here Kiliani passed the gate, through which, only little later, Emil Fischer arrived at the stereochemistry of the sugars. Kiliani, with his experiments, turned the key twice and, thereby closed it again; he would have had to turn only once to open it."
- [70] B. Tollens, *Kurzes Handbuch der Kohlenhydrate*, J. A. Barth, Leipzig, **1895**; further editions in 1898, 1914 and 1935 (revised by H. Elsner).
- [71] E. Fischer, *Untersuchungen in der Puringruppe* (1882–1906), Springer, Berlin, **1907**.
- [72] E. Fischer, B. Helferich, *Ber. Dtsch. Chem. Ges.* **1914**, 47, 210.
- [73] E. Fischer, *Untersuchungen über Aminosäuren, Polypeptide und Proteine* (1899–1906), Springer, Berlin, **1906**.
- [74] E. Fischer, *Untersuchungen über Depside und Gerbstoffe* (1908–1919), Springer, Berlin, **1921**.
- [75] *Nobel Lectures Including Presentation Speeches and Laureates Biographies, Chemistry, 1901–1921* (Ed.: Nobel Foundation), Elsevier, Amsterdam, **1966**, pp. 15–39.
- [76] See [46], quotation from p. 2130.

