van't Hoff–Le Bel Centennial

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O. Bertrand Ramsay, *Editor*

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FOREWORD

The ACS SYMPOSIUM SERIES was founded in 1974 to provide a medium for publishing symposia quickly in book form. The format of the SERIES parallels that of its predecessor, ADVANCES IN CHEMISTRY SERIES, except that in order to save time the papers are not typeset but are reproduced as they are submitted by the authors in camera-ready form. As a further means of saving time, the papers are not edited or reviewed except by the symposium chairman, who becomes editor of the book. Papers published in the ACS SYMPOSIUM SERIES are original contributions not published elsewhere in whole or major part and include reports of research as well as reviews since symposia may embrace both types of presentation.

PREFACE

For most chemists a pamphlet by J. H. van't Hoff and an article by J. A. Le Bel published within two months of each other in the Fall of 1874 mark the birth of the science of stereochemistry. It is not surprising therefore to note that chemists have been responsible for the organization of symposia or the publication of special commemerative journal issues to mark the van't Hoff–Le Bel centenary. In the December 1974 issue of *Chemical Technology*, E. L. Eliel briefly reviewed the contents of some of the symposia held and articles published in the centennial year (*1*). For the purposes of this volume, the citations found there to papers concerned with the history of stereochemistry will be repeated here as well as others that have come to my attention. About half of the papers that have appeared are concerned with either the origin or significance of the concepts of van't Hoff (*1, 2, 3, 4, 5, 6*) or Le Bel (*7*). Others contain retrospective histories of stereochemistry (*8, 9, 10*), conformational analysis (*11, 12, 13*), molecular models (*14, 15*), or related topics (*16*).

Two recent issues (*17*) of *Tetrahedron* are devoted to the discussion of contemporary developments in sterochemistry. The first issue also contains a reprint of the English translation of Louis Pasteur's 1860 lectures on molecular asymmetry.

The present volume derives largely from papers presented at the van't Hoff–Le Bel Symposium. The symposium included sessions concerned with contemporary aspects (sponsored by the Division of Organic Chemistry) and historical developments (sponsored by the Division of the History of Chemistry) of stereochemistry. This volume includes seven of the papers presented in the latter sessions. The paper by Ramsay that is included here is based on a talk presented at the centennial banquet held on the evening of September 11. The banquet was followed by the premiere of a reading of "Drehen and Spalten," a stereochemical playlet written by Paul Karrer (who received the Nobel Prize in Chemistry in 1937) while a student in Alfred Werner's laboratory at the University of Zurich in 1911. The cast for the performance consisted of many of the symposium speakers plus a few other chemists of note. Since this play can only be fully appreciated in performance, the script and commentary will not be published here. A brief discussion and excerpts from the play are included in *Chemistry* (*18*).

Though the beginnings of the systematic study of stereochemistry might well be dated from 1874, this dating often obscures our understand-

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ing of prior stereochemical investigations and speculations. In the first paper in this volume, Jane Miller discusses some of the ideas considered earlier in the century and in particular those developed by the French chemist and crystallographer, M. A. Gaudin. Although Gaudin put forth some interesting proposals concerning the relationship between crystal shape and molecular architecture, his ideas remained virtually unknown to chemists in the middle of the 19th century. This may seem surprising in view of the fact that Gaudin illustrated his ideas with many graphic formulas and models. In the early part of the century he had shown how Avogadro's ideas could be used to reconcile Dalton's atomic theory with Gay-Lussac's results; but numerous experimental and theoretical difficulties prevented chemists from accepting Gaudin's ideas. By the 1860's, however, when the atomic weight problem had been resolved, Gaudin's sterochemical ideas received little attention, partially because his molecular formulas were not based on the valency theory but rather on symmetry considerations much as Dalton's had been earlier.

There were, however, numerous other practical, theoretical, and philosophical problems that had to be cleared away before chemists considered speculations about molecular arrangement a legitimate part of their science. As Trevor Levere states in the second paper, ". . . an awareness of the ideas of atoms and their arrangement was a necssary but not a sufficient condition for the formulation of stereochemical theories." The positivistic philosophy of Auguste Comte may have contributed to the reluctance of some scientists to speculate too deeply. Many chemists felt that the inner arrangement of the atoms in molecules was unknowable or at least could not be known from chemical studies. By the 1860's even the atomic theory itself was questioned. van't Hoff himself was interested in Comte's philosophy. This interest led him to read William Whewell's "History of the Inductive Sciences," first published in 1837. It is improbable that van't Hoff's reading of this work had any profound influence on his later speculations, but it is interesting to note the following excerpt from the book since Whewell was one of the few scientists of the first half of the 19th century who even commented on Dalton's interest in the geometrical arrangement of atoms in molecules:

> Mr. Dalton himself represented the compound atoms of bodies by symbols, which professed to exhibit the arrangement of the elementary atoms in space as well as their numerical proportions; and he attached great importance to this part of his scheme. It is clear, however, that this part of his doctrine is not essential to that numerical comparison of the law with facts, on which its establishment rests. These hypothetical configurations of atoms have no value till they are confirmed by corresponding facts, such as the optical or crystalline properties of bodies may perhaps one day furnish (*19*).

In his book, "The Philosophy of the Inductive Sciences," Whewell is a bit more critical of Dalton's theory as it relates to crystal symmetry. "It need not surprise us that the theoretical arrangement of atoms does not explain the facts of crystallization; for to produce such an explanation would be a second step in science quite as great as the first, the discovery of the atomic theory in its chemical sense" (*20*). These quotes then illustrate some of the conceptual problems chemists had to overcome before stereochemical speculations were considered legitimate. Other contributing factors are discussed in Levere's paper.

It was van't Hoff's attempt to understand the optical properties of lactic acid that led him to his stereochemical theory. Why was it then that Wislicenus was unable to see the solution since he had been grappling with the lactic acid problem for a number of years? He himself had seen that this was where the solution should be found. "Facts such as these force us to explain the difference between two isomeric molecules which have the same structure by means of different arrangements of their atoms in space." Nicholas Fisher convincingly shows us in his paper that the problem was much more complex than the text-book histories would lead us to believe. Fisher suggests, for example, that Pasteur's work on molecular dissymmetry may have had little impact in the stimulation of further research. Those who were concerned with the problem of isomerism found it difficult to disentangle structural isomers from optical isomers. Wislicenus was faced with numerous experimental difficulties so that even after many years of investigation he was left with the apparent existence of not merely two, but four, lactic acid isomers. "Wislicenus got himself trapped in an experimental dead end as well as a theoretical dead end," to quote a summary sentence from Fisher's article.

It is not surprising therefore to find that Wislicenus greeted van't Hoff's ideas with great enthusiasm. Wislicenus was also influential in bringing van't Hoff's ideas to the attention of the chemical world. Other chemists, however, were either indifferent or hostile to van't Hoff's proposals. Some of the experimental and theoretical reasons that formed the basis of these objections are traced in the first of H. A. M. Snelder's two papers. For example, one of the experimentally based objections was derived from Pasteur's earlier report of the existence of an optically inactive, non-resolvable form of malic acid. A colleague of van't Hoff, J. W. Bremer was finally able to demonstrate experimentally that this was not the case and van't Hoff was able to show how his new stereochemical theory could be used to solve the problem.

Le Bel has received far less attention from historians than van't Hoff, and he therefore remains somewhat obscure as to his contributions to stereochemistry. The ideas of van't Hoff and Le Bel are contrasted in the second of Snelder's papers.

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Most chemists would assume that the use of molecular models play an important role in the formulation and development of stereochemical ideas. Yet the history of the use of models has not been well documented by historians. In my paper I attempt to consider the consequences of the use of models in the early history of stereochemistry. The models prepared by van't Hoff in 1875 may have served to make his ideas more comprehensible to a chemical world that was not accustomed to the visualization of molecular geometries. The kind of models used by van't Hoff do not seem to have been widely used in subsequent decades; rather chemists turned to the tetrahedral models first prepared by Auguste Kekulé in 1867 and later modified by Adolph Baeyer in the 1880's. It has generally been assumed that ball-and-spring models were used in the 1880's to illustrate Baeyer's Strain Theory. With reference to these kinds of models, however, it has been difficult for contemporary chemists to understand how it was possible for Baeyer to consider cyclohexane both strained and planar. A closer examination of the models used by Baeyer reveals that he had legitimate reasons for his view and that the use of these models by other chemists until early in the 20th century may have contributed to prevalence of the planar cyclohexane ring in the chemical literature.

The structure of cyclohexane was also tied in with the structure of benzene; and Baeyer contributed significantly to the experimental investigations which were directed toward the solution of the benzene problem. The reconcilliation of the theory of the tetrahedral carbon atom with the planar structure of benzene occupied the interests of many chemists (such as Baeyer) throughout the remainder of the 19th century. Tonja Koeppel discusses some of the difficulties encountered in the formulation of a stereochemical theory in the absence of an adequate theory of bonding.

As the basic tenants of sterochemistry became better established, the way was paved for more dynamic theories: the precursors of conformational analysis. However, the experimental and theoretical complications that accompanied the introduction of these ideas accounts for their lack of acceptance in the late 19th and early 20th centuries. G. V. Bykov discusses the early experimental and theoretical studies of C. A. Bischoff who attempted to establish a basis for the existence of conformational isomerism in acyclic systems. Bischoff even devised a graphic formula to illustrate these conformers that closely approximated the presently used Newman projections. Since his ideas could not be experimentally verified, Bischoff has faded into obscurity in the connection with the origins of conformational analysis. van't Hoff himself recognized that if rotation about the carbon–carbon single bond were not free, certain phases [conformations] of the molecule might be favored. Since no such conformational isomers were known, van't Hoff was forced to assume that for all practical purposes the rotation was free. P. H. Hermans suggests that most chemists in the early 20th century simply did not read van't Hoff's ideas concerning the possibility of conformational isomerism, or if they did, they saw little relevance to their work. Most organic chemists in this period were not interested in undertaking or considering the physical–chemical studies that might have confirmed the existence of a rotational barrier. Hermans himself was one of the few that did undertake such studies in the 1920's and established the existence of a rotational barrier in one acyclic system. He, along with H. G. Derx and others in Delft, also provided convincing experimental evidence of the multiplanar structure of cyclohexane. But again the time was not ripe, and these studies remained almost unknown by the 1940's during the birth of conformational analysis.

The reasons for the delay in the acceptance of multiplanar forms of cyclohexane (first proposed by H. Sachse in 1888) are discussed in some detail by Colin Russell. Experimental studies that were originally perceived ". . . to be simple tests for the theory proved later to be concerned with a whole complex of variables, not just one." It seemed that only by about 1950 had the relevance of the Sachse–Mohr theory become apparent to a sufficiently large number of organic chemists to change the nature of stereochemistry to its more dynamic phase.

Prior to this period most chemists seemed to be working out the consequences of static stereochemistry. These accomplishments were by no means negligible, however. One of the major extensions of stereochemical theory was into the area of inorganic chemistry. George Kauffman relates the circumstances surrounding the resolution of the first inorganic coordination compound in 1911 in Alfred Werner's laboratory. The resolution of a completely inorganic compound three years later finally established that carbon need not be present for a compound to be optically active. Werner's triumph signalled the beginning of rapid advances in inorganic chemical research.

The significance of stereochemical concepts was not lost on investigators in other fields. John Parascandola discusses some of the earlier applications in the area of pharmacology. By the turn of the century, for example, ". . . chemists and pharmacologists began to associate the paralyzing properties possessed by onium salts with the change from a planar structure to a three-dimension structure." The difference in pharmacological activities of cis–trans isomers was also noted. In the early decades of the 20th century, Arthur Cushny undertook investigations concerning the pharmacological activity of enantiomeric species. By the 1930's a number of theories had been proposed and experimental work undertaken to attempt further to explain the specificity of drug action in stereochemical terms. The increasing activity in this area as the century

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progressed contributed to the dramatic impact of the publication of Barton's paper in 1950.

After 1950 there was a rapid change in the nature of stereochemical research; even the terminology had changed dramatically. One of those who contributed significantly to the change of character of stereochemical research was V. Prelog. In the paper which he has contributed to this volume, he recounts his own involvement with R. S. Cahn and C. K. Ingold in the development of an unambiguous method of denoting the configurational arrangement of groups about an asymmetric carbon atom. The R/S system withstood the tests and modifications so well that it found its way into organic textbooks within a few years of the publication of the joint paper in 1966.

It may be hoped that the reader of the papers in this volume may find a new appreciation of the present state of stereochemistry from the perspective of the past.

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1

M. A. Gaudin and Early Nineteenth Century Stereochemistry

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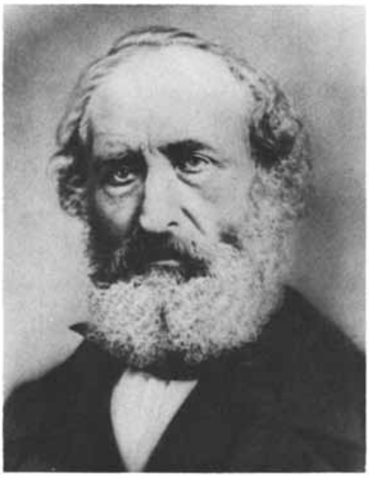
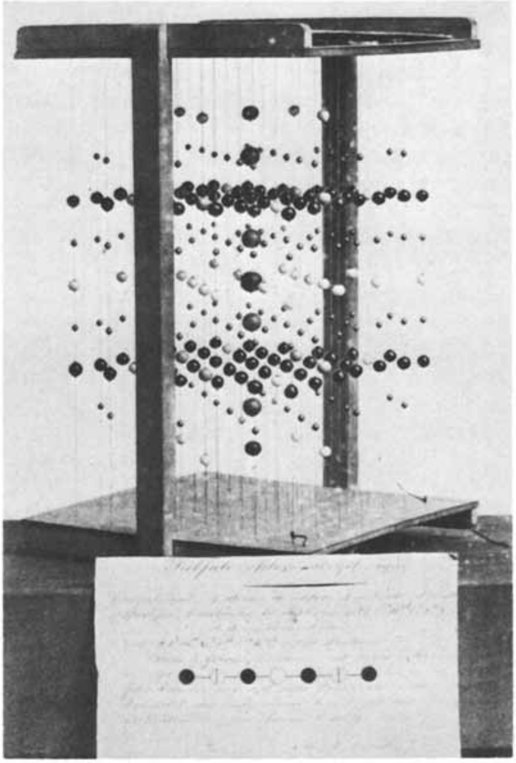
The synthesis of a viable theory of the arrangement of atoms in space depends upon three major elements: 1) the acceptance of atoms as real entities occupying and arranged in three dimensional space, 2) the integration of concepts and experimental methods which provide correct formulas for compounds and generally accurate atomic weights, and 3) an understanding of the ways in which atoms combine, their affinities or valency. The work of Marc Antoine Gaudin illustrates the development of a theory of stereochemistry, which made use of the first two elements and which solved some of the problems of early nineteenth century chemists, but which, primarily because it did not concern itself with valency or chemical properties, had little influence on contemporary scientists (1-5).

Gaudin's theory on the nature of atoms and molecules and their arrangement in space grew out of lectures given by Ampere at the College de France in 1827 (6). Gaudin states, "It was M. Ampere who first attracted my attention to the subject, but (my theory) is not treated in the same manner and different conclusions have been drawn (7)." Gaudin's theory was first expressed in his notebook in a manuscript entitled, "Chimie Generale - hypothesis sur la constitution des atomes (1828) " It indicated that the purpose of his work was to determine the arrangement of atoms in molecules and in the three forms of matter and, thereby, to explain physical properties. This goal did not change throughout his life and the publication, in 1873, of his book, "L'Architecture du Monde des Atomes (8)," presented a theory which was little different from that in his first notes.

The title, "The Architecture of the World of Atoms", shows Gaudin's firm belief in the real exist-



Marc-Antoine Gaudin 1804-1880



Chlorostrychnic sulfate

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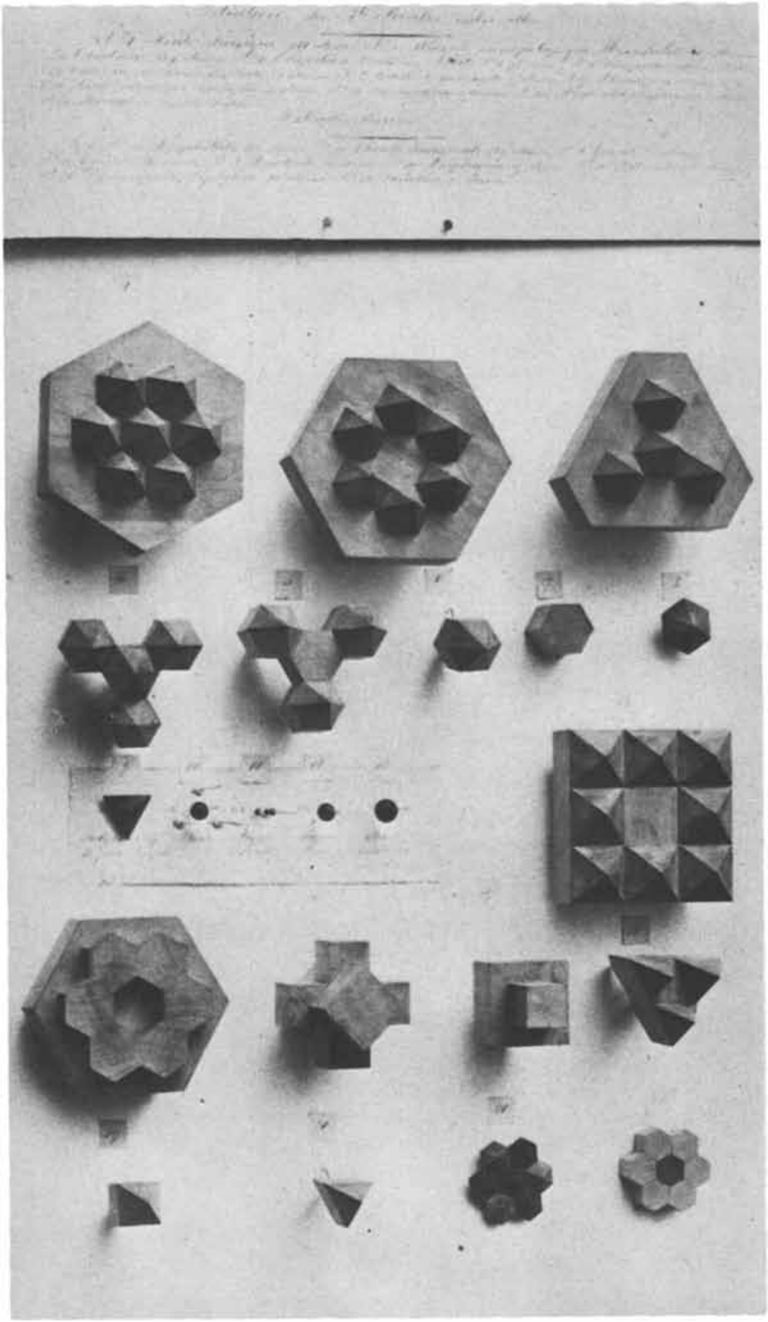
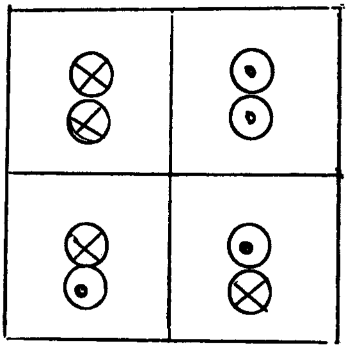
ence of atoms as the building blocks of chemistry. In the "General Chemistry" he defines atoms as fundamental parts of matter, indivisible, unalterable and spheriod. His adoption of the form of the sphere, because it is the most symmetrical form, the easiest to use in calculations, and the one which causes no problems when constructing geometrical crystals, illustrates the fundamental criteria he employed in developing his theory. Gaudin acknowledges his debt to Dalton's "ingenious hypothesis" (9) and feels that the atomic theory holds the hope for the advancement of chemistry. Dalton's view of the enormous number of particles in the atmosphere (10) is expanded by Gaudin to a calculation of the number of atoms (8×10^{20}) in a metallic cube with a side of 0.002 meters (11). Gaudin conceived of an atom as constantly in motion "as a mathematical result of all the ethereal undulations which act upon it in time from the abyss of infinite space. (12)" All physical properties such as gravity (pesanteur), heat and electricity are the result of the difference of the percussion of the particles of ether on the surface of the chemical atoms. Gaudin explains the appearance of calm in matter as the formation of molecules in which the atoms are placed in equilibrium positions. Harmony is developed by regularity in the construction of the molecules.

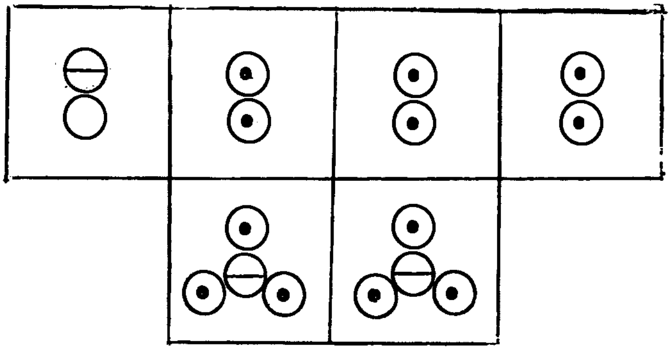
The first task for Gaudin in establishing his theory of matter was to simplify the language of chemistry by giving a clear definition of atoms and molecules (13). An atom is an indivisible smallest part of matter (14) and a molecule is an isolated group of atoms with no set number or nature (15). (Later in the "Architecture", Gaudin does postulate that all atoms are constructed from ether (16).) Gaudin then attacks the problem of the relation between weight and density. Because each atom and therefore each molecule has its own constant weight, the density of a compound must depend upon its arrangement in space (17). He accepts Ampere's (Avogadro's) hypothesis that at the same pressure and temperature, molecules of gases are at the same distance from one another (18). Ampere's paper (19) stated, "that from consequences deduced from the theory of universal attractions, considered as the cause of cohesion, and the facility with which light travels through transparent objects, it must be concluded that the atoms (Ampere calls them "molecules") of matter are separated by great distances." Ampere considered "molecules" as combining into "particles" with a minimum number of four "molecules" per particle forming a polyhedron. Crystals are built



up from these particles in a definite manner, the form of the crystal depending on the form of the particle (20). However, Ampere treats atoms as mathematical units, the particle, or first distinguishable form of a compound, being of greatest importance and, although the conclusions he draws explained correctly the law of combining volumes, the insistence on polyhedral forms for molecules was confusing. (In 1835 (21), Ampere modified his definition of matter. He finds three constituents, particles, molecules and atoms. The particle is the infinitely smallest portion of matter which has a recognizable physical form. Molecules are an assembly of atoms held at a distance by the attractive and repulsive forces of each atom. Atoms are material points from which emanate attractive and repulsive forces.) Gaudin rejected Ampere's four particle molecule (22) and successfully explained Gay-Lussac's law in modern terms by showing that the molecules of most gaseous elements were biatomic (23). He explained the formation of hydrogen chloride as the combination of a biatomic molecule of chlorine with a biatomic molecule of hydrogen to form two molecules of HCl (24).



To form ammonia, one biatomic molecule of nitrogen reacted with three biatomic molecules of hydrogen to form two tetratomic molecules of ammonia (25). (Note that Gaudin uses Daltonian symbols for the elements.)



Gaudin perceived that by considering gases, such as oxygen, as biatomic, many of the problems of structure and atomic weights could be solved. Making use of Dumas' vapor density measurements (26), he was able to determine the number of atoms in the gaseous molecules of many elements (Mercury is monatomic, iodine is biatomic and a molecule of sulfur has six atoms.) and to present a table of corrected atomic weights (27). He was also able to determine the correct formulas for several oxides, including those of boron and silicon. The recognition of the formula, SiO_2, was particularly important to crystallographers and to the development of Gaudin's theory. The law of Dulong and Petit seemed to confirm Gaudin's atomic weights. Notebook pages dated 1828 show Gaudin determining specific heats of metals and using vapor densities to calculate atomic weights and the number of atoms present in a molecule of vapor (28).

By using these new values, Gaudin found a numbercial relationship between the weights of elements with like combining properties. The ratio of weights in a series appears to be 1,2,5,8,13,15 and this held true for the halogens; oxygen, sulfur, selenium and tellurium; nitrogen, phosphorus, arsenic, and antimony; the known alkali metals and alkaline earths; and copper, silver and mercury. A study of the atomic weights led Gaudin to draw up relationships between the weights of elements and the physical properties, such as physical state, fusibility, conductivity, etc., of the elements and their compounds (29). (Earlier (30) Ampere had produced a classification of elements based upon their physical and chemical properties and Gaudin would have been likely to try to refine this.)

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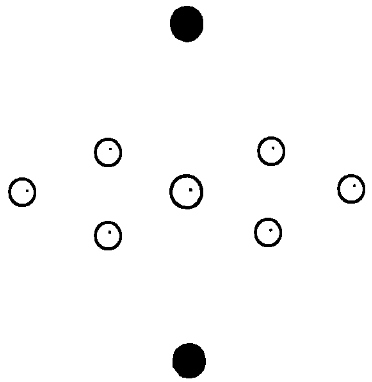
Therefore, for Gaudin, the fundamental property of an atom,which could explain all others, was its weight and he concluded that atoms were held together in molecules or in crystals by a force proportional to their weight. In a manuscript dated Frebruary, 1831, he calculated the force holding together the rows of atoms in metals by determining the maximum weight a wire of known thickness would support (31). Gaudin thought that when atoms combined, they would be most likely to form regular polyhedra and that chemical combination is only the coming together (mise en commun) of a certain number of atoms to form groups made stable by their mutual equilibrium (32). The distance between atoms and between molecules is the result of two forces, one attractive and the other repulsive, dependent upon the movement of the ether (33). The forms of products in a reaction have no relation to the forms of the compounds or elements from which they are made. In the act of combination real atoms come together to form a regular geometric solid by the symmetrical disposition of atoms. The reason for combination is a geometrical one (34).

Thus, Gaudin's theory was close to that of Dalton in his firm belief in the existence of atoms of definite weight, held together by Newtonian forces and forming regular geometrical molecules. He has not, however, adopted Dalton's concern about the repulsion of like atoms. The atoms in Gaudin's compounds are simply placed in the most symmetrical arrangement. Gaudin's theory also rejected other fundamental ideas of Ampere. Ampere conceived of chemical combination as interpenetration of two particles so that their centers of gravity will be at the same point (35). Ampere's explanation of the attractive and repulsive forces operating between atoms is certainly clearer than Gaudin's, however, Ampere considers atoms as material points, from which these forces emanate (36). Gaudin also rejected the dualism in Ampere's theory (37). He felt that molecular structure was the result of atoms arranging themselves symmetrically in order to counterbalance the enormous forces of the ether and emphasizes that these forces exist in all directions resulting in a molecular architecture which is three dimensional.

Crystallography became the major element in Gaudin's development of his theory (38). He acknowledges that Hauy had founded mineralogy, but states that it has been proven that cleavages and "decroisements" are powerless in certain cases to determine the primative molecule and, above all, the inward arrangements of atoms (39). In Gaudin's first work, he rejected the "cubic" atoms of Hauy (40) and later proclaimed that he had discovered the true law to explain Hauy's theories (41). Gaudin's notebook contains copies of requests to Delafosse and to Dumas for crystals to analyse and to Faraday for some pure graphite. (There is no evidence that Gaudin ever received a degree from the College de France. He worked as a calculator for the Bureau des Longitudes and was associated with no laboratory.) Gaudin also used isomorphism in salts to determine the crystalline systems of a given molecule (42-43), feeling that Mitscherlich's results helped support his own theory. During the 1830's Gaudin began experimenting with the production of artificial minerals and was successful in making excellent rock crystal, sapphires, etc. He accomplished this by the fusion of salts at very high temperatures (44-46). Could this have been the ultimate proof to Gaudin of the correctness of his theory, for the extreme heat should have been able to separate the atoms of the reacting compounds so that they could mingle and rearrange into the most symmetrical form?

In summary, Gaudin felt that the structure of matter was determined by the formation of the most symmetrical configuration of atoms grouped without regard to affinity or dualistic considerations. On combination the atoms regroup into the most aesthetic form. An unstable substance will try to rearrange to a less unsymmetrical state and reaction is caused by the creation of a more stable arrangement. A biatomic molecule consists of two spheriod atoms spinning rapidly around each other like double stars. A triatomic molecule will be in a straight line with the odd atom placed in the center unless all three atoms are alike, in which case, a planar equilateral triangle is formed. For a molecule with the formula 1A, 3B (a letter indicates a single kind of atom), an equilateral triangle centered with the odd atom is produced; for 1A, 4B, a tetrahedron; 2A, 4B, an obtuse octahedron. When more complex molecules are formed, units of odd numbers of atoms are used as building blocks, arranged in lines and slices (tranches), and the greater the number of these combinations possible in all directions, the more stable the compound. Crystals, which show accord with experimental cleavage and measured angles, may be constructed from these molecules, however Gaudin seems to work from aesthetic considerations rather than adopting, as Ampere did, Hauy's primative forms. Gaudin often checked the accuracy of chemical analyses by trying to construct a model of the molecule and included the water of crystallization in his structures as an integral part of the molecule.

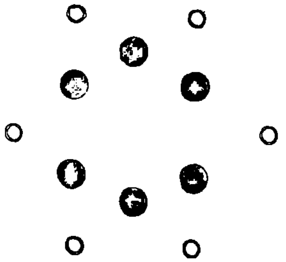
Because of his interest in crystals, Gaudin was at first little concerned with organic chemistry, but felt that the laws which govern the arrangement of atoms were the same for organic and mineral molecules (47). In an early communication he corrected Berzelius' experimentally determined formula for benzoic acid on the basis of structural arguments (48). In 1847 he used his theory to verify the formulas of alcohol and ether and describes alcohol as an example of a compound, 1A, 2B, 6C. The oxygen A being single, and the heaviest, will occupy the center of the molecule; each carbon B will align itself with an oxygen opposite each other: and the 6 hydrogens, C, will be arranged symmetrically and in equilibrium placed in a plane perpendicular to the axis passing through the central atom so that each is an equal distance from A and B. This forms a double pyramid with a regular hexagon for a base (49).

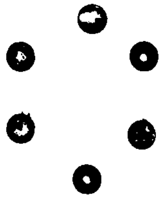


In 1851 he determined a structure for stearic acid using combinations of three atoms, 1A, 2B, such as hydrogen bicarbon, to fill space (50). The following year he presented a paper to the Academy of Sciences, showing that he could incorporate organic molecules into the same system as minerals (51).

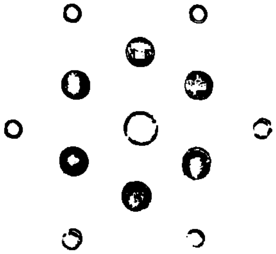
In 1865, after many unsuccessful attempts to have his research accepted in the "Annales de Chimie" or other prestigious journals, Gaudin published a pamphlet explaining his theory, particularly as it applied to organic chemistry (52). He states that marsh gas (CH_4) must be in the form of a tetrahedron(53,54).

He represents benzene as a hexagon of carbon atoms surrounded by the six hydrogens forming another hexagon or with two hydrogens perpendicular to alternating carbons (55).

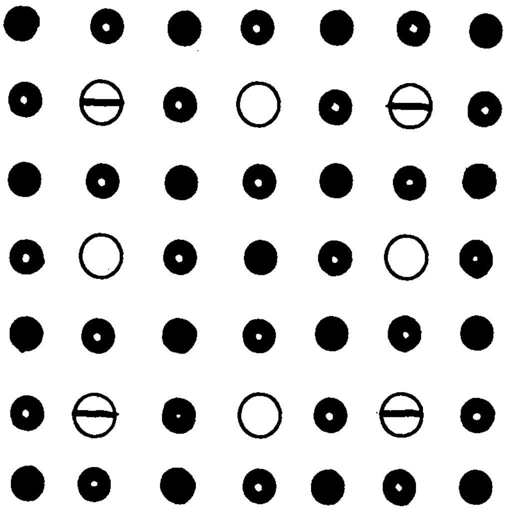




The oxygen contained in phenol simply occupies the center of the carbon hexagon.



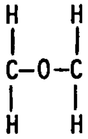
Gaudin recognized the presence of $-CH_2$ groups in organic molecules, and describes hydrocarbons as being formed from links of these groups, however, their purpose was to satisfy the condition that all molecules are decomposible into linear elements, lines of atoms, parallel between themselves, composed of 3,5,7 or 9 atoms. To illustrate these principles, he constructs a model of strychnine (56,57).



o represents H; •, C; O, oxygen; Θ, N.

At the request of Joseph Henry, who had read the 1847 paper, Gaudin prepared models of compounds illustrating his theory for exhibit in the Smithsonian. Unfortunately, the models were destroyed in a fire in 1865, however photographs of some of them are in existence (58).

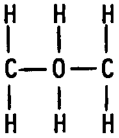
In 1867 Gaudin presented a paper to the Academy, attempting to show that Wurtz's ideas on the arrangement of atoms and on saturation were incorrect (59). Gaudin states that he is not able to admit any foreign intervention capable of producing the least deformity into the groups of atoms making up compounds as a part of general mechanics. To illustrate this he uses the structure of the glycols. He defines the principal element of organic compounds as the carbhyde (CH_2), which has not been isolated. (Can we infer that Gaudin believed this unit to have an independent existence, as does water?) If the molecule contains one oxygen, it is added to the center to give an aldehyde or acetone.



$$\begin{array}{ccc} H & & H \\ | & & | \\ C & -O- & C \\ | & & | \\ H & & H \end{array}$$

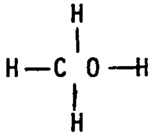
Aldehyde

Add a molecule of water and you will obtain an alcohol.



$$\begin{array}{ccccc} H & & H & & H \\ | & & | & & | \\ C & — & O & — & C \\ | & & | & & | \\ H & & H & & H \end{array}$$

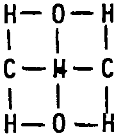
Alcohol



$$\begin{array}{ccccc} & & H & & \\ & & | & & \\ H & — & C & O & —H \\ & & | & & \\ & & H & & \end{array}$$

Methyl Alcohol

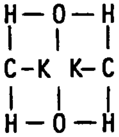
Glycols are formed by the addition of two oxygen atoms



$$\begin{array}{ccccc} H & — & O & — & H \\ | & & | & & | \\ C & — & H & — & C \\ | & & | & & | \\ H & — & O & — & H \end{array}$$

Glycol

Substitution in a glycol took place in the following manner:

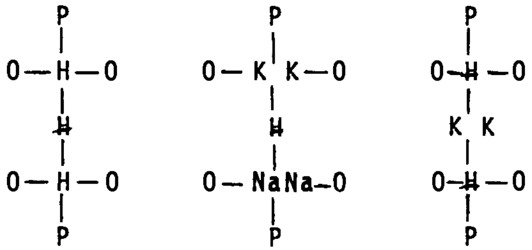


$$\begin{array}{ccccc} H & — & O & — & H \\ | & & | & & | \\ C & -K & & K- & C \\ | & & | & & | \\ H & — & O & — & H \end{array}$$

Potassium Glycol

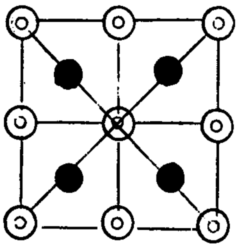
Gaudin did admit that in a mono or polybasic acid, there is an effective and local substitution of one atom of metal (or double atom of alkali metal) for a double atom of hydrogen. He felt that hydrogen might have a unique status in chemistry because of its small atomic weight.

Using the phosphates, Gaudin shows how substitution can take place and how compounds change in form, according to his theory:

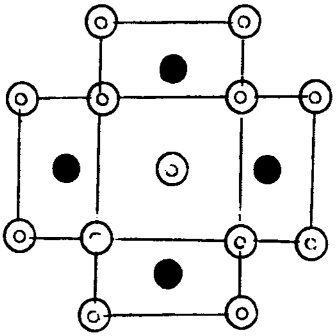


Note that he doubles the formula of phosphoric acid to make the molecule more symmetrical. Later Gaudin complained of the irregularity produced in compounds in which one atom is simply substituted for another in the same position (60). Whenever substitution takes place the molecule will change its form to satisfy the rigorous equilibrium conditions necessary in all regions. In discussing the controversy between Hofmann and Berthelot over doubling volumes, Gaudin emphasizes that the atomic composition in vapor as well as in liquids and solids is the most important fact to know.

In 1869 Gaudin attacked the problem of the sugars and was forced to find different structures for the same empirical formula (61). He explains the difference between cane sugar and fruit sugar by the differing arrangement of atoms.

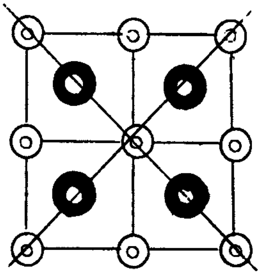


cane sugar

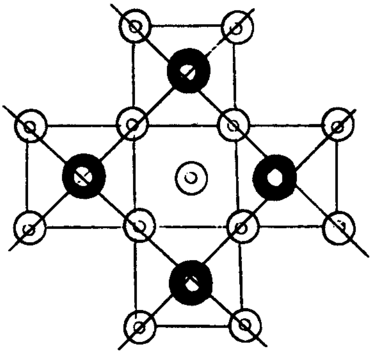


fruit sugar

He assumes that these compounds are literally carbohydrates, constructed of carbon atoms and water molecules and notes that the water must be separated from the carbon. He also compares these forms with those of epidote and garnet, proving, to his satisfaction, that his theory was consistent throughout nature.

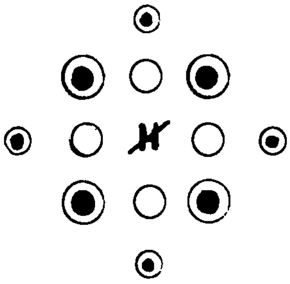


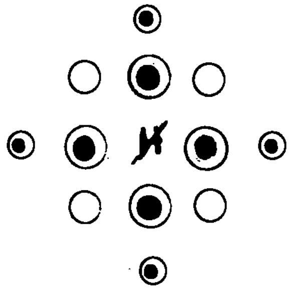
epidote



garnet

In the "Architecture", Gaudin explains the optical isomerism of the tartaric acids by constructing two possible forms (62).





Gaudin doubles the molecule, placing the carbons inside or outside the central network, thus producing different optical rotation. He notes that racemic acid is a mixture of the two tartaric acids and contains two additional molecules of water and, therefore, postulates its structure as an unstable compound of the two tartaric acids chained together by the water of crystallization.

Although Gaudin's system was able to solve some problems in both organic and inorganic chemistry, it was obviously limited in that the chemical properties of compounds were seldom considered. If nineteenth century chemists had read Gaudin seriously they could have received an appreciation for atoms arranged in three dimensional space and a respect for the value of atomic weight determination and the adoption of the correct formulas of compounds based upon the number and kind of atoms present. Both van't Hoff and Le Bel recognized Gaudin's accomplishments, van't Hoff thinking that Gaudin had been close to solving the problem of the relative positions of atoms in molecules (63), and Le Bel using his principles to determine the conditions of equilibrium in carbon compounds. (64).

Portions of this paper have been presented at the 154th meeting of the American Chemical Society, Chicago, Sept. 1967 and the Midwest Junto of the History of Science Society, University of Oklahoma, April 1969. I am greatly indebted to Gaudin's grandsons, the late Dr. A. M. Gaudin of M.I.T. and M. Albert Gaudin of Versailles, France for providing me biographical information and access to Gaudin's papers. The Joseph Henry correspondence was located with the assistance of Mr. Louis Pearson of the Smithsonian Institution. The collection of the French manuscripts was supported by a travel grant from the Research Funds of the University of Missouri-St. Louis.

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2

Arrangement and Structure—A Distinction and a Difference

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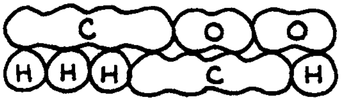
At this celebration of the hundredth anniversary of two seminal papers by the founders of stereochemistry, Jacobus Henricus van't Hoff[1] and Joseph Achille Le Bel[2], I want to ask why views like those expressed in their papers were so long delayed, or, more fruitfully, why previous chemists, possessing most of the fragments which would be used to create the concepts of stereochemistry, came nowhere near the achievements of 1874. They did not try and fail, but instead they deliberately avoided concepts which might now seem akin to stereochemistry as one would avoid deserts, bogs, and other dangerous and misleading regions.

Let me state the problem more fully. Stereochemistry involves what van't Hoff in the title of the first publication of his paper called 'the extension into space of the structural formulae at present used in chemistry'. Note in passing something to which we shall have to return: most apparently structural formulae prior to the mid-1870s were not intended to express the spatial arrangement of atoms. This is implied in van't Hoff's title, and is confirmed time and again by his predecessors[3]. Kekulé, who appears to have used structural formulae if anyone in the 1860s did so, was at pains to explain that his rational formulae were reaction formulae[4]. They were initially and primarily classificatory in function[5]. Kekulé's formulae, however, in common with almost everyone else's, except Benjamin Collins Brodie's in his calculus of chemical operations[6], presented molecules as being made up of atoms, as for example in this representation of acetic acid:

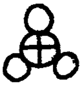
In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.



[7]

For all the perennial doubts through the nineteenth century about the existence of atoms[8], almost all chemists recognized what J.B. Stallo in 1881 called 'the merits of the atomic hypothesis as a graphic or expository device'. He rightly went on to remark that 'It is a fact beyond dispute that chemistry owes a great part of its practical advance to [the use of the atomic hypothesis], and that the structural formulae founded upon it have enabled the chemist, not merely to trace the connection and mutual dependence of the various stages in the metamorphosis of "elements" and "compounds", so called, but in many cases (such as that of the hydrocarbon series in organic chemistry) successfully to anticipate the results of experimental research'[9].

So stereochemistry involves the atomic theory and the concept of structure where this means the arrangement of atoms in space. It is well enough known that the concepts of atomism and of something like structure were implied simultaneously in chemical literature in 1808 in John Dalton's *A New System of Chemical Philosophy*. The last part of the volume presents the atomic theory, and ends by stating that 'when three or more particles of elastic fluids are combined together into one, it is to be supposed that the particles of the same kind repel each other, and therefore take their stations accordingly'.[10] The consequence was that he represented 'An atom of sulphuric acid, 1 sulphur + 3 oxygen' by the characters



[11].

Of course this is a very limited notion of structure, but others were advanced which were more sophisticated. Wollaston, for example, published a paper in 1808 in which he applied Dalton's law of multiple proportions to super-acid and subacid salts. He found an unexplained gap in the potassium oxalates, and argued that an understanding of the interaction of elementary atoms would require not only arithmetical laws but also a geometrical conception of the relative arrangement of atoms in three dimensions[12]. Examples of such speculations could be multiplied[13]. Now if stereochemistry involves the ideas of atoms and their arrangement, and if these ideas were broadly familiar to chemists from 1808, then critical ingredients were at hand. Why were van't Hoff and Le Bel not anticipated long before 1874? The answer is not simple, and I shall merely suggest some of its components. Of course my strategy will be to argue that awareness of the ideas of atoms and their arrangement was a necessary but not a sufficient condition for the formulation of stereochemical theories, and to try to probe the area of insufficiency. If one assumes that atomism offered at least a useful hypothesis to most of the community of chemists after 1808, then concentration on the concept of arrangement should best illuminate the area of insufficiency. Easy access to this area is provided by one of the nineteenth century's most brilliant chemists, Auguste Laurent, in the preface to his *Chemical Method* of 1854[14]. Laurent there identified two stumbling blocks in the way of establishing a chemical system -- facts, and their causes. If one restricted oneself to facts, then no true system would be possible, and one could achieve only a descriptive natural history of chemical species organized according to a natural classification[15]. Although Laurent did not say so at this point, he clearly believed that natural classifications were sterile, and advocated an artificial system[16]. Mere facts were inadequate for chemical science. What of the other stumbling block? Laurent wrote:

'By setting out from the idea of causality, or of atoms and their arrangement, we must determine in any particular body, which of its atoms are combined simply, which of them are combined intimately, whether they are copulated or conjugated...

But intermediate between facts and their causes, we have generalities and laws. Would it not be possible, by relying upon them, to establish a *method*, that is to say, a system of formulae, a classification and a nomenclature, having the advantage of systems based upon facts, and of those based upon hypotheses, but without their inconveniences.

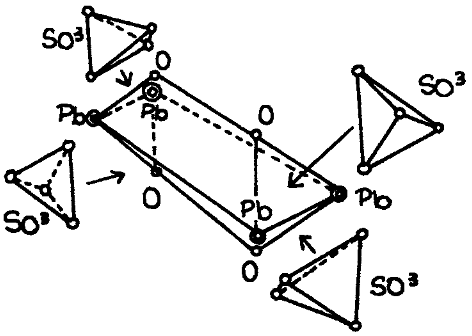
This is what I have attempted to do in this work, by endeavouring to render it as much as possible independent of all hypotheses. Such of them as are to be met with are isolated, and may be left entirely on one side, without any detriment to the progress of the work.

...I do not...reject the research after causes, although these may form perhaps but a perpetual mirage, destined to impel us incessantly to an exploration of new countries.'[17]

Laurent's identification of causality with 'atoms and their arrangement' was unfortunate for arrangement, implying that it was probably undiscoverable. It could serve a heuristic function, but the search for the actual arrangement of atoms in molecules was likely to be long if not eternally frustrated. What Laurent has to say about arrangement is therefore not very different from what Auguste Comte has to say about causation in general -- it serves its purpose during the adolescence of a science, but has no place in the final positive edifice of laws[18]. Comte was Laurent's contemporary. I have no grounds for claiming any influence of one on the other, and many of Laurent's speculations went beyond Comte's positivism, but the extent of their common ground is striking[19]. They both recognized that the inner arrangement of molecules was unknown, and, in the present state of chemistry, unknowable, so that whatever classification one adopted could serve only as a convention and a guide[20]. Laurent and Comte admittedly differed in their choice of classification. Comte felt that electrochemical dualism offered the most appropriate guide to the classification of chemical substances and to the prediction of their reactions[21], while Laurent rejected the doctrines of Berzelius and instead proposed his own nucleus theory[22]. In neither case, however, was method supplanted by ontology. Gerhardt could have been speaking for both of them when he wrote: '...we have a deep conviction that all the metamorphoses of a single substance are controlled by general laws, which we can scarcely envisage today, but which the united efforts of chemists will certainly succeed in discovering...

We have been taken to task with a sort of disdain for performing chemical algebra; we are glad to accept this description, because we believe that the true progress of science does not consist of limitless multiplications of facts and experiments, but in establishing analogies, and generalizing them by formulae, thus finding the laws which are the only guides to the certain prediction of phenomena.'[23]

The concept of arrangement was useful -- it provided Laurent with the seminal idea behind his nucleus theory[24], brought chemistry and crystallography closer together[25], and underlined the unity of organic and inorganic substitutions[26]. Thus he proposed, for example, a representation of lead sulphate inferred from crystallographic evidence[27], in which lead oxide and sulphuric acid maintained their independent existence within an overall regular structure. Fisher[28] has intepreted Laurent's description through this diagram:



But in spite of such attempts, arrangement was for Laurent primarily a heuristic concept which provided *general* ideas. As Laurent stated in 1845, it was impossible to represent a three-dimensional atomic arrangement by a linear formula[29]. One should therefore leave to others the search for formulae indicating arrangement, attacking them as long as they failed to find *true* formulae. Instead, assuming that substances with similar but individually unknown arrangements should have similar properties, one could create a system of synoptic formulae, expressing *analogies*. As for arrangement, Laurent concluded, 'Shall we always be ignorant of [it]? Who knows?'[30]

A knowledge of the detailed arrangement of atoms in molecules was thus at least temporarily ruled out by positivist attitudes towards science among precisely those chemists whose thought might otherwise have been inclined to consider arrangement.

The same attitudes, reinforced by polemical bias, ruled out an aspect of atomism, which, incorporated in the theory of valency, was to be essential for the development of stereochemistry. I am referring to the concept of affinity[31]. Comte rejected it as metaphysical, and therefore unscientific[32]. Laurent[33] admitted that the nature of atoms, presumably including their affinities, influenced molecular properties, but stressed that arrangement was of greater importance than atomic natures. The wide-ranging successes of the theory of types, with its structural conceptual basis, distracted attention from the concept of chemical affinity[34], which had provided the eighteenth century with its most successful classificatory tool and furnished the basis for Berzelius's electrochemical dualism. Since the theories of dualism and types were generally, if mistakenly, seen in opposition to one another, and since the theory of types was becoming dominant in mid-nineteenth-century organic chemistry, affinity ceased to be a prominent topic in that realm of chemical discourse. Dumas was one of the principal villains in the temporary demise of affinity[35], and seems to have recognized and enjoyed his role. In the 1850s and 1860s several chemists, including Daubeny[36] and Wurtz[37], correctly emphasized this aspect of recent chemical history.

So far I have argued that those who adopted a unitary theory neglected affinity and were agnostic about arrangement. Their neglect of the former and agnosticism about the latter were not of course wholly polemical or philosophical. Crystallographic analogies had led to theories suggesting constitutional analogies but as Beudant pointed out in 1843[38], crystallographers had learned caution and were primarily concerned to establish a classification based upon the external characteristics of bodies, and not upon internal ones. Then too, as competent mineralogists like Dana were well aware[39], it was all very well to say that in principle chemical and crystallographic classifications should agree, while in practice it was hard to see how they did so. At the very least, the doctrines of preformation in chemistry and in crystallography alike would need modification. There were hopes, expressed by Laurent[40], Gerhardt[41], Baudrimont[42], Kekulé[43], and others, that crystallography would one day reveal the relative positions of atoms in compounds -- but of course, as Baudrimont[44] and Kekulé[45] stressed, these would be positions in unreacting compounds. Reactions would change structures, and accordingly information derived from reactions could not lead to direct knowledge of structures. Laurent accordingly used synoptic formulae, e.g. $C^8H^2Cl^4O + O^2$ for chloracetic acid[46], Kekulé used reaction formulae;[47] and so on, quite properly, since chemists were concerned with predicting chemical changes and classifying chemical species. Williamson's brilliant work on etherification showed both the success and the limitations of a dynamic approach, expressed by the twin equations:

$$\frac{\begin{matrix}H\\H\end{matrix}SO^4}{\begin{matrix}C^2H^5\\H\end{matrix}O} = \frac{\begin{matrix}H\\C^2H^5\end{matrix}SO^4}{\begin{matrix}H\\H\end{matrix}O} \text{ and } \frac{\begin{matrix}H\\C^2H^5\end{matrix}SO^4}{\begin{matrix}H\\C^2H^5\end{matrix}O} = \frac{\begin{matrix}H\\H\end{matrix}SO^4}{\begin{matrix}C^2H^5\\C^2H^5\end{matrix}O}\,.$$[48]

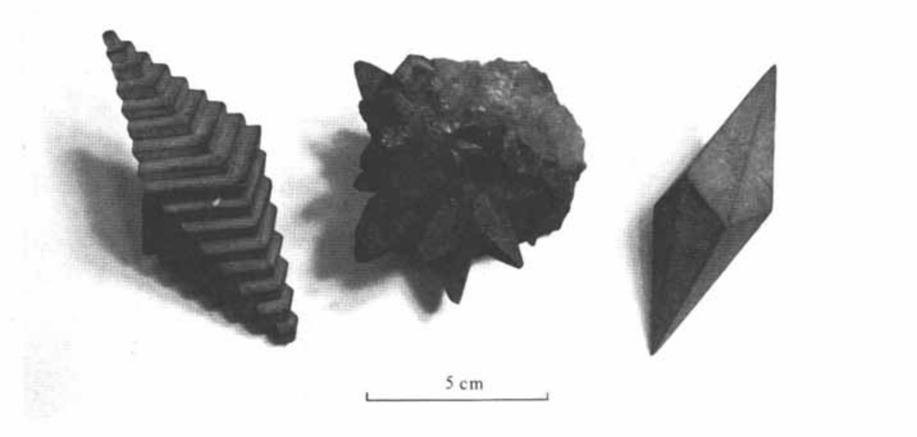
Kinetic theory, with its associated chemical kinetics -- Berthelot's *Mécanique Chimique* -- may have seemed to point the same way.

Thus, although substitution and the rest seemed to encourage the view that arrangement was the principal determinant of properties, awareness of chemical change made knowledge of arrangement seem unobtainable. Besides, phenomena other than substitution were not so easily handled. For example, compounds produced by burning diamond and charcoal respectively in oxygen were indistinguishable[49], but the ease with which carbon dioxide was produced was very different in the two cases, and even if one claimed that charcoal and diamond were chemically the same species, they were physically distinct. Berzelius in 1840 characterized such variations as instances of allotropy[50], and went on in 1845 to suggest that this was not rare, but was probably a general property of the elements. He suggested that allotropes of a given element were different states of that element, but made no reference to arrangement as underlying the differences[51]. Laurent quickly provided the missing structural speculations, writing to Berzelius that there was a great analogy between their respective views. 'The atom, according to its definition, cannot be modified; different varieties of a simple body α, β, γ, can therefore only be different groups. That, if I have understood it aright, is the consequence of your hypothesis. As I see it, the chemists' ordinary atom would be a group of elements, and different groups of these elements would constitute the varieties α, β, γ.'[52] Berzelius provided no illustration, and thought such speculation highly premature: 'It is impossible to account for the cause of the difference of simple bodies, according to their allotropic state, even if we could determine the properties possessed by each state. Does the difference perhaps reside in a particular grouping of the atoms of simple bodies, in such a way, for example, that 2, 3 or several atoms would combine to form groups of atoms which would play the part of a single atom, as seems to be the case with sulphur? or is an electric polarity modified or fixed up to a certain point...? Our present knowledge does not allow us to answer these questions.'[53] It was not even clear that these different states should be classified as representing the same element. Brodie, for example, analyzed graphite oxide, applied Dulong and Petit's law, and found that the atomic weight of graphite was 33. He concluded that this form of carbon 'should be characterized by a name marking it as a distinct element'[54]. And yet there were some who regarded isomerism and allotropy as analogous phenomena, both explicable in terms of arrangement[55], even while isomerism itself remained perplexing to many. William Odling in 1864 told the chemical section of the British Association for the Advancement of Science that

> 'Isomerism is, in fact, the chemical problem of the day...It is curious to note the oscillations of opinion in respect to this subject. Twenty years ago the molecular constitution of bodies was perceived by a special instinct, simultaneously with, or even prior to, the establishment of their molecular weights. Then came an interval of scepticism, when the intimate constitution of bodies was maintained to be not only unknown, but unknowable. Now we have a period of temperate reaction, not recognizing the desired knowledge as unattainable, but only as difficult of attainment. And in this, as in many other instances, we find evidence of the healthier state of mind in which, now more perhaps than ever, the first principles of chemical philosophy are explored. Speculation, indeed, is not less rife and scarcely less esteemed than formerly, but is now seldom or never mistaken for ascertained truth.'[56]

Perhaps it will be appropriate to leave the mid-century proponents of theories emphasizing arrangement with the reflection that trends such as Odling discusses, reflecting the changing status of imagination in science, may for a while be more important for the progress of science than substantive discoveries. After Gerhardt came to Paris in 1838, Liebig continued to send him advice, warning him that the Academy was 'the implacable adversary of theories'[57]. Even Dumas had suffered from theorizing, and if Gerhardt wanted to indulge himself, Liebig admonished, 'For the love of God, don't write about theories, except for German journals!'[58] Later, Kolbe's blast[59] against van't Hoff's stereochemical nonsense was to be countered by the latter's assertion that imagination in the 1870s was not playing 'the role that it is capable of playing; even today Kepler would have been able to raise himself as high above his surroundings as in his own time'.[60]

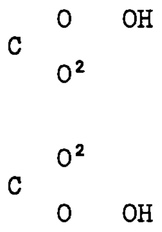
So much, for the time being, for arrangement and speculation. What of electrochemical dualism with its emphasis upon atomic natures? Briefly, as Dumas wrote in 1840[61], it is a theory which seeks in principle to derive the fundamental properties of bodies from the nature of their elementary particles. Within it, arrangement is therefore secondary. Its emphasis upon atomic polarities, and its corresponding binary classification suggest a series of polar linkages, so that if one thinks of arrangement one is likely to do so in terms of order, links in a chain, rather than arrangement, bricks in a three-dimensional edifice. Berzelius, architect and champion of electrochemical dualism, was willing to consider more nearly structural notions. On one occasion he even went so far as to propose that organic atoms had a certain mechanical structure, 'which enables us to deprive some of them of certain elementary atoms without altering the whole very much'. Thus milk sugar, 8O + 10C + 16H, could be converted to mucic acid, 8O + 6C + 10H, by the removal of four carbon atoms and six hydrogen atoms[62]. Such speculations may on occasion have proved useful to Berzelius, but when he came to consider specific problems in which structural notions might have been useful, he clearly regards the mutual satisfaction of electrochemical affinities as the determining factor, to which notions involving arrangement can lend at best circumstantial support. For example, in 1839 Berzelius wrote to Pelouze[63] that he had asked the Academy in Stockholm: 'What is the greatest number of oxygen atoms which can be combined in a single oxide with a single or compound radical?' Yet he makes no mention of geometric distribution, and it seems likely that he was thinking merely in terms of combining proportions and the mutual satisfaction of electrochemical affinities. A more striking instance is provided by Mitscherlich's discovery of the principle of isomorphism in Berzelius's laboratory in 1819[64]. Berzelius initially hesitated to accept isomorphism, but checked Mitscherlich's results at first hand, and was convinced[65]. He wrote to the crystallographer Haüy, whose theory was contradicted by



Calcite crystals and models (ca. 1805) illustrating Haüy's theory. Photograph by G. L'E. Turner.

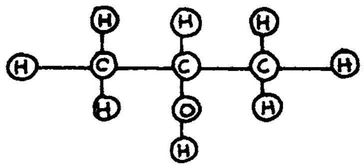
Mitscherlich's findings, and who therefore remained unconvinced[66], that 'A new field is opening here, we are becoming aware of a whole new class of substances which, while conserving absolute regularity of their form, can vary in their elements between certain limits, without this variation being determined by chemical affinity, and without it conforming to the law of chemical proportions; it derives from the simple circumstances that these different substances can form integrant parts of the same crystalline form'[67]. Isomorphism clearly had much to contribute to chemical and crystallographic theory, and Berzelius did allow it to modify his mineralogical classification, but in a characteristic and significant way. In his *Attempt to establish a pure scientific system of mineralogy by the application of the Electrochemical theory and the Chemical Proportions* of 1814, he had arranged minerals according to the electrical character of their positive constituents. Once Mitscherlich had demonstrated isomorphous replacement among these constituents, Berzelius's classification became invalid, and in 1824 he proposed a new system -- this time based on the electrical characteristics of the *negative* constituents[68]. Ideas involving structure might have something to tell chemists, might even occasionally point out errors -- but although structure and relativity were intimately connected, Berzelius's classification was always based upon the nature of atoms, whose forces interacted to produce the secondary phenomena of arrangement.

Theories which greatly depreciated either notions of arrangement or notions of atomic natures could not support stereochemical ideas, which needed both atoms and arrangement. So the theory of types and electrochemical dualism had either to merge or to give way altogether before the concept of stereochemistry could become possible, let alone credible for the community of chemists. The two theories were in fact modified and merged, gradually, and as early as 1853 Liebig was able to write to Gerhardt, 'It is very strange that the two theories, formerly quite opposed, are now combined in one which explains all the phenomena in the two senses'[69]. Radicals had ceased to function for chemists as the all but immutable organic analogues of inorganic elements, and might even suffer substitution to occur. The theory of types, on the other hand, was modified so as to allow for the role of individual atomic natures in determining molecular properties[70]. Merging, however, was not enough. The structural aspects of the theory of types had initially been derived from crystallographic analogies, based upon the concept of a fundamental nucleus. Other and earlier crystallographic analogies had used the concept of close packing to derive structure. Neither approach sufficed for the development of stereochemistry, which emerged after the development of valence theory, and direction valence theory at that[72]. The theory of types was useful here: but the theory of types provided above all a classification which was artifical[73]. What was needed was a description which was realistic. That is why van't Hoff in 1874 wrote: 'It appears more and more that the present constitutional formulae are incapable of explaining certain oases of isomerism; the reason for this is perhaps the fact that we need a more definite statement about the actual position of the atoms'[74]. As his statement implies, formulae illustrating relations of valency were already widely assumed to convey some information about the relative disposition of atoms. The tetravalency of carbon had been variously established, by Odling, Kekulé, Kolbe, Frankland, and Couper[75]. Pictorial representations of compounds of tetravalent carbon raised important questions, for they appeared to represent the physical disposition of atoms. Crum Brown[77] was among the first to pursue such questions critically. Kekulé came by the early 1860s to a position where he believed that 'it must now indeed be held as a taste of natural science to ascertain the constitution of matter, and therefore, if we can, the position of the atoms'[78], and although he refused to reach premature conclusions about stereochemistry, his views came to be seen as supportive of the stereochemical enterprise. The formal introduction of the notion of structure came, however, not from Kekule, but from Butlerov, who asserted in 1861:

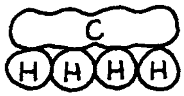


$$\begin{array}{lll} & O & OH \\ C & & \\ & O^2 & \\ & & \\ & O^2 & \\ C & & \\ & O & OH \end{array}$$

(A.S. Couper)



Crum Brown



Kekulé

[76]

'Starting from the assumption that each chemical atom possesses only a definite and limited amount of chemical force (affinity) with which it takes part in forming a compound, I might call this chemical arrangement, or the type and manner of the mutual binding of the atoms in a compound substance, by the name of "chemical structure"[79]. The achievement of van't Hoff and of Le Bel was largely that of furnishing a conceptual tool which would enable chemical structure to be represented systematically and with precision. They refined the theory of structure and did indeed provide 'a more definite statement about the actual position of the atoms'. When Butlerov five years later defined structure as the arrangement of chemical bonds between atoms in a particle[80], he was being both comprehensive and retrospective.

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3

Wislicenus and Lactic Acid: The Chemical Background to van't Hoff's Hypothesis

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We are celebrating the publication one hundred years ago of important and similar papers by two young chemists. The ideas in these papers are often conflated in a discussion of the so-called "Le Bel - van't Hoff theory of the asymmetric carbon atom," but as van't Hoff himself was the first to point out, the two theories were different in origin and approach - that is, in the questions that they were designed to answer: 'On the whole, Le Bel's paper and mine are in accord; still, the conceptions are not quite the same. Historically the difference lies in this, that Le Bel's starting point was the researches of Pasteur, mine those of Kekulé' (1). In other words, van't Hoff remained within the purely chemical tradition of the structure theory, while Le Bel was heir to a longstanding tradition of seeking the connexion between crystalline form and chemical and physical properties. This had begun early in the nineteenth century with the work of Haüy and Biot, and was continued by Ampère, Gaudin, Baudrimont, Laurent, de la Provostaye, and Pasteur (2); it remained almost exclusively a French pursuit, and it made very little impact on the mainstream of chemistry until well after 1874 (3).

In discussing the situation in chemistry when van't Hoff's famous paper was published in that year, let me first make the point that though chemists were aware of the physical phenomenon of optical activity in mid-century, they did not think it of much importance. In 1841 Gerhardt, who clearly did not share the crystallographic interests of many of his fellow-Frenchmen, had inveighed against those who saw any chemical significance in optical activity:

> Certainly no chemist would dispute the chemical identity of natural camphor and the camphor regenerated by the action of caustic potash on Delalande's oil of camphor, despite the fact that these two camphors differ in rotatory power... We chemists require chemical differences to distinguish between two bodies, and it therefore seems to me that those who attach such great importance to rotatory power are deluding themselves strangely if they look to it for the future of

In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

chemistry (4).

As I have maintained elsewhere (5), the main business of organic chemists in the middle of the nineteenth century was differentiation between isomers; this is implied in the above quotation from Gerhardt. But chemists followed Gerhardt in being extremely selective about which cases of isomerism they would consider chemically significant; and at a time when there was no satisfactory explanation of chemical isomerism (that is, of ordinary structural isomerism), it is hardly surprising that chemists shied away from the additional complications that would have resulted from acknowledging differences between optical isomers. Much to Biot's disgust (6) chemists continued to regard optically active laurel camphor as identical with inactive lavender camphor; the first thorough investigation of dextro-, laevo- and inactive camphor was carried out by the physicist Chautard (7), and it was not followed up by chemists.

Again, Pasteur's classic work on the resolution of the tartrates of 1847-49 was certainly noted at length in Liebig and Kopp's Annual report on the progress of chemistry, but in the physics section, under "Optics" (8), abstracted by Friedrich Zamminer, Professor of Physics at Giessen, and himself interested in the optical properties of biaxial crystals (9). Pasteur's discovery received comparatively little notice in the organic chemistry section, either at the time (10) or during the next twenty-five years. The one man who might have established optical activity as a phenomenon important to chemists, Pasteur himself, largely turned his attention to the more fertile study of fermentation after his appointment to the University of Lille in 1854.

Nor was there much more interest in the phenomenon in the 1860s. In 1865 Wanklyn discussed the isomerism of primary and secondary alcohols in his article "Isomerism" in Watts' Dictionary of Chemistry, and then went on: 'A more superficial kind of difference was noticed by Pasteur, some years ago, between varieties of amylic alcohol... Chemists are not agreed how these varieties are to be regarded, it being still uncertain whether a mere difference in action upon polarised light points to any but the very slightest difference in constitution' (11).

In 1863 Carius introduced the term "physical isomerism" to describe those cases where substances which are chemically identical differ in such physical properties as optical activity or heat of formation; but he introduced it with the important modifier "only": 'Tribromoallyl and tribromohydrin should certainly be considered as only physical isomers, and the same is the case for a large number of bodies which are noted for their different influence on polarised light...' (12). As a chemist he clearly attached little importance to physical differences of this sort. His "physical isomerism" caught on, however, and by the end of the century the term was in general use (13).

To repeat, then, chemists in the middle of the nineteenth century were aware of optical activity, but did not think it very significant (14). This throws some doubt on the standard accounts of the origins of stereochemistry, from which it can appear that Pasteur's work was at the forefront of chemists' minds in the 1860s and early 70s, and that it was his problem that they were trying to solve (15). It is important to realize that this was not the case, and that there were plenty of purely chemical problems at this time which were difficult enough without such added complications. I am not trying to deny that optical activity was ultimately important to van't Hoff - without it he would of course have made no suggestion of the asymmetric carbon atom - but clearly he was not primarily concentrating on the chemical explanation of optical activity; rather, as he made clear in one account of the origin of his theory (16), he was confronting the usual chemical problem of differentiation between isomers, specifically the isomers of lactic acid that Wislicenus had long been investigating.

It was no coincidence that in the papers of both Le Bel and van't Hoff lactic acid was the first concrete example of an optically active compound that they discussed after their theoretical introductions (17). Lactic acid, $C_3H_6O_3$ or $CH_3.CH(OH).COOH$, is the simplest natural product occurring in an optically active form, and most important it had long been at the centre of chemical controversy, and had been exhaustively investigated. By 1869 Wislicenus at least was convinced that the number of genuine lactic acid isomers exceeded that allowed by the existing structural theory, and that therefore this isomerism could only be explained by an extension of structural formulae to show 'the arrangement of atoms in space' (18) - though as I shall show he did not then mean what van't Hoff later meant by the same famous phrase.

I shall devote most of the rest of this paper to discussing the long history of lactic acid, and showing how Wislicenus was eventually forced to the conclusion that the possibilities of the existing theory were exhausted, and that an extension was necessary. Apart from the fact that lactic acid was the specific inspiration for van't Hoff's new theory, it is always helpful when discussing a complicated and confused period in the history of chemistry to choose some typical or paradigm case, and follow the fortunes of some particular research; lactic acid is an eminently suitable example not only because of the many theoretical discussions of its chemical nature but also (and no less important) due to the many practical difficulties surrounding its examination from the beginning of the nineteenth century up to about 1874. Thereafter, its chemical nature was regarded as essentially established (19), and chemists turned their attention to more complex molecules.

The Early History of Lactic Acid

Lactic acid was first isolated by Scheele in 1780 when he precipitated the calcium salt from sour milk, filtered it, and recovered the acid by adding oxalic acid. Though he recognized it as an individual acid, not to be confused with acetic, he thought it an intermediate product in the formation of vinegar: 'It seems destined, if I may so speak, to be vinegar; but, from the want of such substances, as, during fermentation, produce some spirituous matter, it seems not to be volatilised'. He therefore mixed it with brandy (which is such a substance) and left it for a month, when vinegar was indeed formed (20). This confirmed his view that lactic acid was merely "imperfect" vinegar.

This view was adopted and extended by the French analytical chemists Fourcroy and Vauquelin, who in 1800 examined "pyromucous, pyrotartarous and pyroligneous acids" [lactic, pyrotartaric and formic] and concluded that these were not individual acids; they (and indeed all organic acids) were merely combinations of acetic acid with various inseparable oils (21). Scheele's observation that lactic acid can be converted into vinegar (separated from its contaminant) was decisive in reaching this view.

The chief difficulty facing these, and all other chemists who attempted to characterize lactic acid, was their inability to obtain a pure sample. Its character of a very hygroscopic liquid long impeded accurate analysis. This is well illustrated by the work of Bouillon-Lagrange in 1804. Not only did he detect nitrogen when he destructively heated his sample and obtained cyanide, but he concluded 'that Scheele's lactic acid is composed of:

Acetic acid.
Potassium chloride.
A little iron, perhaps, held in solution by acetic acid.
And some animal matter.'(22)

In view of these difficulties, it is astonishing that in 1807 Berzelius was able to recognize the presence of lactic acid in muscle juice simply by reference to its general properties as established by Scheele and Lagrange (23). Nor is it surprising that when Braconnot examined the fermentation products of grain extracts in 1813, he believed he had obtained a hitherto unknown acid, which he called "nanceic", after Nancy, where he worked (24). He thought it a component of Lagrange's lactic acid - a conclusion which is clearly correct.

Berzelius was perhaps the first to get away from the idea that lactic acid was a mixture of acetic acid with an adulterant, even if this change was at first cautious. In his Jahresbericht for 1822 and 1827 he maintained that there was true compound formation between acetic acid and the other (animal) component of lactic acid, hence the difficulty in separating them (25). But by 1832 he was convinced that acetic acid was not present as such in lactic acid, either as a mixture or as a compound; lactic acid is far too stable when heated (26). This work (the first paper published in the first issue of Liebig's Annalen) ensured that hereafter lactic acid would be studied in itself, rather than as a modification of acetic acid. During the 1830s new preparations of the acid were also discovered by Mitscherlich, Frémy and others (27); these yielded lactic acid in sufficient purity and in sufficient quantities for its chemical properties to be investigated. In 1833 Gay-Lussac and Pelouze measured the physical properties, noting the hygroscopic nature of the pure acid, and carried out the first accurate quantitative analyses of the acid and its salts (28). Perhaps most important, they discovered the property of forming lactide (as the dimeric anhydride was later called by Gerhardt) on heating lactic acid to 250°. This was perhaps the first acid anhydride (as opposed to the anhydrous acids of the dualistic electrochemical theory) to be discovered in organic chemistry. The property of lactide-formation was unique, and might have served as a characteristic test for lactic acid, but it seems never to have been used as such; methods of identification remained very uncertain. For instance, when Liebig in 1837 identified the acid in sauerkraut as lactic acid (29) he relied on no firmer identificatory evidence than that the fermentation appeared similar to others in which lactic acid was formed, and that the zinc salt had the appearance of zinc lactate. Despite the ready availability of lactic acid, Pelouze was able to complain in 1845 that its chemical properties were very little known, compared with those of many other compounds of far less intrinsic interest (30). This situation was corrected by Pelouze himself and, to a far greater extent, by Liebig and his Giessen pupils in the late 1840s.

One of the major difficulties facing Liebig with his stress on a programme of organic analysis for his students (31) was the lack of agreement on any characteristic test for lactic acid. Most of the tests commonly used would give positive results with a large number of different natural acids, since most relied on the insolubility of one or more of the lactates; lactic acid was particularly confused with phosphoric, whose salts have very similar solubilities. In a discussion of false identifications of lactic acid, Liebig's pupil Strecker particularly censured the French chemists Pelouze, Boussingault and Gobley for identifying the acid in intestinal juice as lactic (32). Partly as a result of this interest on the part of one of his Assistants, Liebig undertook a re-examination of the components of muscle juice, which had not received any serious study since Berzelius identified lactic acid 'on such unknown and feeble grounds' (33) forty years before.

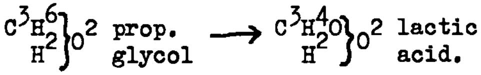
Liebig concluded that muscle lactic acid was essentially identical with fermentation lactic acid, as Berzelius had claimed, the only slight difference being less water of crystallization in the zinc and calcium salts of the former compared with those of the latter. He dismissed this as insignificant, and probably attributable to the fact that he had obtained the former crystals by evaporation, and the latter by cooling (34). But obviously sufficient doubts remained for his pupil Engelhardt to re-examine the differences between the salts of the meat and milk acids; he found that the differences in water of crystallization were not due to accidents of preparation, as Liebig had supposed, but were intrinsic. And there were other, even more striking differences, for instance in the ease with which water of crystallization was driven off, and in solubility in water and alcohol (35):

Zinc (meat) lactate	Zinc (milk) lactate
9 hrs. heating at 100° required to drive off water of crystallization.	Water of crystallization driven off rapidly at 100°.
Dissolves in:	Dissolves in:
2.88 pts cold water	6 pts cold water
5.7 pts hot water	58 pts hot water
2.23 pts cold alcohol	Insoluble in alcohol, hot or cold.
2.23 pts hot alcohol.	

Not unnaturally Engelhardt concluded that two isomeric modifications of lactic acid existed, and he speculated that the ordinary milk acid, which he found to be dibasic, was the dimer of the meat acid (36). This idea gained some support later (37). Heintz confirmed Engelhardt's experimental results (though he did not agree with his theoretical conclusions), and coined the name "paralactic acid" for the meat acid (38). This slowly gained general acceptance, though the alternative "sarcolactic acid" (from the Greek for flesh) was often used. It was Heintz's interest in lactic acid that was responsible for his pupil Wislicenus' pursuing this topic that he was to make very much his own.

In 1850 Strecker synthesized lactic acid from acetaldehyde-ammonia, via alanine (39). This was one of the first syntheses of a naturally-occurring organic substance, for though Wöhler had synthesized urea in 1828, few other natural products were obtained synthetically for many years. Thus when Strecker succeeded in synthesizing lactic acid it was an occasion for excitement, and interest in the substance and in its chemical nature immediately increased. It was the subject of very extensive investigation in the 1850s, and in particular it was the focus of a long and rather futile quarrel about its chemical nature between Kolbe and Wurtz, representing respectively the radical theory of Liebig and Berzelius, and the type theory of Gerhardt (40). This argument was more semantic than substantial: it centred on the significance to be attached to chemical formulae, and on how chemical properties should be expressed. It would take too much time, and it would lead me too far from my consideration of the experimental investigation of lactic acid, to do any justice to this argument, but the essentials were as follows:

On theoretical grounds, Wurtz considered that lactic acid was dibasic, since in 1858 he obtained it by the controlled oxidation of the dihydric alcohol propylene glycol:

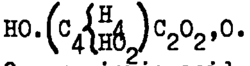


$$\left.\begin{matrix}C^3H^6_2\\H^2\end{matrix}\right\}O^2 \text{ prop. glycol} \longrightarrow \left.\begin{matrix}C^3H^4_2O\\H^2\end{matrix}\right\}O^2 \text{ lactic acid.}$$

His formula contains two replaceable hydrogen atoms (<u>41</u>). He was attacked by Kolbe who on equally theoretical grounds considered lactic acid to be propionic acid in which a hydrogen atom in the radical had been replaced by hydroxyl (though such a replacement was not experimentally possible at the time):

$\mathrm{HO.(C_4H_5)C_2O_2,O}$

Propionic acid

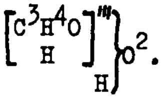


$$\mathrm{HO.}\left(\mathrm{C_4}\left\{\begin{array}{l}\mathrm{H_4}\\ \mathrm{HO_2}\end{array}\right.\right)\mathrm{C_2O_2,O.}$$

Oxypropionic acid (lactic).

Since the hydroxyl replaced a hydrogen atom within the radical, it was relatively inactive, and lactic acid was therefore monobasic (<u>42</u>). On the basis of further a priori arguments, Kolbe also denied Wurtz's interpretation of the glycols as containing two alcoholic groups (<u>43</u>), and claimed that the alcohol equivalent to lactic acid would be an <u>isomer</u> of propylene glycol.

Under pressure from Kolbe, Wurtz conceded that lactic acid was monobasic, but still maintained that it was "diatomic" - that is, that it was derived from the double water type and had two centres of reactivity; under certain circumstances, a second hydrogen atom could be replaced. Ultimately, in 1861, he reached the conclusion that lactic acid contained both an alcoholic and an acidic group, essentially the modern position. Being caught within the framework of the type theory, however, he had no means of expressing this clearly; all he could do was to show when necessary that there was <u>some</u> difference between the two replaceable hydrogen atoms:

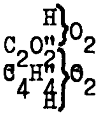


$$\left.\begin{array}{r}\left[\begin{array}{c}\mathrm{C^3H^4O}\\ \mathrm{H}\end{array}\right]'''\\ \mathrm{H}\end{array}\right\}\mathrm{O^2}.$$

(<u>44</u>).

Kolbe, on the other hand, never gave any ground at all in this debate, nor did he ever abandon his search for <u>the</u> absolute formula, as opposed to Wurtz's several formulae, which were merely comparative. As with so many controversies in the history of science, we can say that both these chemists were half-correct in their view of the chemical nature of lactic acid, but that it was impossible for them to separate the valid from the invalid in their respective positions.

It was very much easier for those who stood outside the controversy to do this. For instance, the English chemist Perkin reached the correct solution earlier than Wurtz, and expressed it more clearly: lactic acid has two halves, 'the former acting as an acid, and the latter as an alcohol':



$$\left.\begin{array}{r}\mathrm{H}\\ \mathrm{C_2O''_2}\end{array}\right\}\mathrm{O_2}\qquad[\text{acid}]$$
$$\left.\begin{array}{r}\text{Ȼ}_4\mathrm{H''_4}\\ \mathrm{H}\end{array}\right\}\Theta_2\qquad[\text{alcohol}]$$

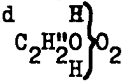
(<u>45</u>).

And two German chemists who were unusual among their countrymen in having converted to the type theory despite having been educated in the radical theory, thus standing apart from both entrenched positions, had come to the same conclusion earlier still; these were Kekulé and Wislicenus.

In the first part of his *Lehrbuch der organischen Chemie*, published in 1859, Kekulé pointed to glycollic and lactic acids as showing the limitation of the conventional theory of types:

> Several cases exist, however, in which different hydrogen atoms which according to the type theory should actually be equal in value, are not in fact so. Thus glycollic acid (and similarly lactic acid) exhibits the behaviour of a monobasic acid, although it contains two typical hydrogen atoms. The two hydrogen atoms of glycollic acid are not identical, although both belong to the type. One behaves exactly like the typical hydrogen of alcohol, and the other exactly like the typical hydrogen of acetic acid. (46).

Unfortunately Kekulé refused to show this difference graphically, but it is clear from other remarks that his conception of the chemical nature of glycollic and lactic acids was essentially complete (47).

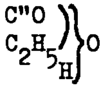
Wislicenus was unusual among chemists of this period in starting his publishing career with three wholly theoretical papers - though admittedly these were not published in one of the primary chemical journals. And thereafter, he generally prefaced his experimental papers with an account of the theoretical ideas which had suggested the work to him, so that it is particularly easy to follow the development of his chemical thought. His third paper of 1859 was a lengthy and explicit attack on the limitations of the current theory of types (48); specifically this theory could not distinguish between the two replaceable hydrogen atoms of glycollic and lactic acids, which besides being monobasic acids were simultaneously monacidic bases. Wislicenus' own formula for glycollic acid  $\left.\begin{matrix} H \\ C_2H_2''O \\ H \end{matrix}\right\} O_2$ was supposed to show that one hydrogen atom (the top one) could be replaced by negative groups, and the other by positive. This convention that the top half of the formula represented the negative portion of the compound was applied throughout organic chemistry (49).

Shortly after Kekulé and Wislicenus, Limpricht, another German adherent of the type theory, adopted much the same view of the chemical nature of lactic acid. He expressed this in a formula very similar to Perkin's (50).

We can take it, then, that by the beginning of the 1860s there was some measure of agreement about the chemical nature of lactic acid, even if the followers of Kolbe were never convinced that it acted simultaneously as an acid and an alcohol. The main problem of the 1860s became to assign it a chemical structure in terms of the structural theory of Kekulé and Butlerov, which became widely accepted in this decade. The major figure in this phase of the story of lactic acid was Wislicenus, who for some twelve years devoted most of the limited time that he could spend in his laboratory to establishing the structure of lactic acid, and also to elucidating the differences between ordinary lactic acid and the modification extracted from meat, which during the arguments of the late 1850s had largely been forgotten (51).

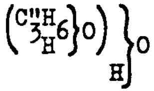
Wislicenus' Theoretical and Experimental Work on Lactic Acid

When Wislicenus started his serious research into lactic acid in 1861, his theoretical position was explicitly intermediary between those of Wurtz and Kolbe. He thought that both of these were right up to a point, but that slavish adherence to either view prevented the full truth from emerging (52). His own formula was, he claimed, derivable equally from propionic acid (following Kolbe) and from propylene glycol (after Wurtz), thus combining the advantages of both schools of thought:



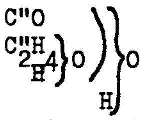
$$\left.\begin{matrix}\left.\begin{matrix}C''O\\C_2H_5\end{matrix}\right\}\\H\end{matrix}\right\}O$$

Propionic acid



$$\left.\begin{matrix}\left(\left.\begin{matrix}C_3''H_6\\H\end{matrix}\right\}O\right)\\H\end{matrix}\right\}O$$

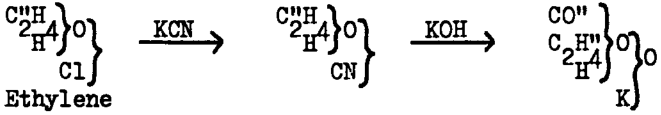
Propylene glycol



$$\left.\begin{matrix}\left.\begin{matrix}C''O\\\left.\begin{matrix}C_2''H_4\\H\end{matrix}\right\}O\end{matrix}\right\}\\H\end{matrix}\right\}O$$

Lactic acid (53).

This formulation led him to concentrate on the central radical C_2H_4OH, which he recognized as an 'incomplete molecule of [ethylene] glycol' (54). Lactic acid, then, 'must be obtainable from ethylene glycol in the same way as propionic acid from ethyl alcohol, that is, through a cyanide intermediate' (55). He converted ethylene chlorohydrin to cyanohydrin, and hydrolyzed this with potash solution:



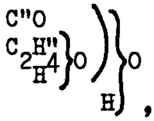
$$\left.\begin{matrix}\left.\begin{matrix}C_2''H_4\\H\end{matrix}\right\}O\\Cl\end{matrix}\right\}\xrightarrow{KCN}\left.\begin{matrix}\left.\begin{matrix}C_2''H_4\\H\end{matrix}\right\}O\\CN\end{matrix}\right\}\xrightarrow{KOH}\left.\begin{matrix}\left.\begin{matrix}CO''\\\left.\begin{matrix}C_2H_4''\\H\end{matrix}\right\}O\end{matrix}\right\}\\K\end{matrix}\right\}O$$

Ethylene chlorohydrin cyanohydrin Pot. lactate.

He obtained a yield of acid which was too small to analyze, but in his first report he had 'not the slightest doubt' that it was lactic acid, on the basis of the appearance of its potassium and zinc salts (56).

Four months later, however, he had revised this firm conclusion; again on the basis of rather meagre evidence, he decided that his acid was <u>para</u>lactic acid. He relied for his identification on the appearance of the zinc salt crystals under the microscope (though he admitted that these were not very different from those of ordinary zinc lactate), and on the percentage of water of crystallization in the zinc salt (57), which had been the basis of Engelhardt's original distinction between lactic and paralactic acids.

Obtaining paralactic acid by a synthesis from which he had expected ordinary lactic acid led Wislicenus to important theoretical conclusions as to the difference between the two acids (58). Each was to be represented by the same formula



$$\left.\begin{matrix} \left.\begin{matrix} C''O \\ \left.\begin{matrix} C_2H_4'' \\ H \end{matrix}\right\}O \end{matrix}\right) \\ H \end{matrix}\right\}O$$

, but the divalent radical C_2H_4'' differed in the two cases; in paralactic acid, which he had just obtained from ethylene glycol, this radical was ethylene, while ordinary lactic acid, which Strecker had originally synthesized from acetaldehyde (59), and which yielded large quantities of acetaldehyde on dry distillation (60), contained the isomeric radical ethylidene, CH_3CH'' (61). He called the two isomers "ethylene lactic acid" and "ethylidene lactic acid" to underline this difference (62).

Obviously this was the only distinction that he could make; these were the only two isomeric structures permitted by the current structure theory, and so Wislicenus was certainly justified in jumping to this conclusion despite the meagreness of the evidence. Such results as he did have seemed to justify the conclusion fully. In fact, he was very conscious of the lack of evidence:

> I would have liked to have done still more research to confirm the identity I have established between ethylene lactic acid and meat lactic acid, but the very low yield has so far prevented me from obtaining enough material. I have repeated the synthesis several times using 20 gm. of ethylene chlorohydrin each time, but I have never obtained more than about one gram of zinc paralactate, of which a significant amount more is lost every time it is recrystallized. In most cases the yield is much smaller than this... (63).

According to a modern source, the yield from this synthesis is 28-31% (64), which suggests that there is a horrible mixture of by-products. Among these is ordinary lactic acid, as Wislicenus himself recognised (65); in fact, I suspect that he never obtained his ethylene lactic acid (or hydracrylic acid, as we would now call it) free from ethylidene lactic acid, which might explain the apparent similarities with paralactic acid. This question of the purity of Wislicenus' samples is important, and I will return to it.

I cannot leave this early phase of Wislicenus' work on the lactic acids without drawing attention to his discussion of the meaning of chemical formulae, which came towards the end of a long report on this research which he published in 1863. Wurtz, following Gerhardt, had maintained that formulae express only analogies; any formula which brings out analogy is permissible, and will be useful in certain circumstances (66). Kolbe on the other hand sought the one absolute formula, the actual constitution of the compound (67). Wislicenus agreed with Kolbe that any one body could have only one constitution, but stressed that different formulae bringing out different features of this constitution were still permissible:

> Even when we will be in a position to discover the *spatial arrangement* of the atoms in a compound, our formulae can at most be *pictures of bodies projected on a plane*. If we want to express those properties of a body that are visible from different sides, then we will need *several pictures, each one drawn from a different viewpoint*. So long as chemical formulae are only pictures of one and the same chemical body drawn from different sides - that is, while they show the more intimate components combined only in a different *order*, and not in a different *manner* of mutual combination, then in my view the most rigorous chemical conscience can make no objection... (68).

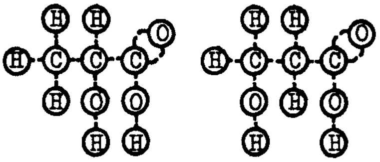
In 1863 Wislicenus was clearly thinking in three dimensions, and looking forward to the day when spatial arrangement of atoms would be susceptible of investigation. His own later remarks about spatial arrangement were not arrived at suddenly. Nor should his welcome for van't Hoff's hypothesis, and for van't Hoff's three-dimensional models (69), surprise us.

Wislicenus' view of the structural difference between the two known lactic acid isomers was maintained for some years. It was supported by the work of his pupil Dossios in 1866, who investigated the difference between ethylene and ethylidene compounds, and showed that on oxidation ethylene lactic acid gives malonic acid, while ethylidene lactic acid (ordinary lactic acid) gives a mixture of acetic and formic acids:

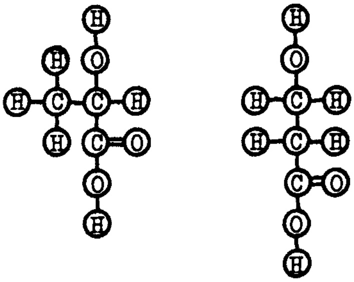
$$\left\{\begin{array}{l}CH_2(OH)\\CH_2\\CO(OH)\end{array}\right. \xrightarrow{[O]} \left\{\begin{array}{l}CO(OH)\\CH_2\\CO(OH)\end{array}\right. \qquad \left\{\begin{array}{l}CH_3\\CH(OH)\\CO(OH)\end{array}\right. \xrightarrow{[O]} \left\{\begin{array}{l}CH_3\\CO(OH)\end{array}\right. + COH(OH) \quad (\underline{70}).$$

[synthetic] meat lactic acid — malonic acid — milk lactic acid — acetic + formic acids

The view that meat and milk lactic acids were respectively β- and α-hydroxypropionic acids was widely accepted - by Crum Brown, for instance, in 1864 (71), and by Frankland and Duppa in 1866 (72), who gave the isomers structural formulae in the modern sense:



Lactic Paralactic
Crum Brown 1864.



Lactic Paralactic
Frankland and Duppa 1866.

Meanwhile, complications were beginning to crop up, which were to disturb this neat view. In 1862 Beilstein discovered β-iodopropionic acid, and when he treated this with moist silver oxide he obtained an acid of formula $C_{12}H_{22}O_{11}$, which he called hydracrylic acid, since on heating it dehydrated to give acrylic acid:

$$\begin{array}{ccccc} C_3H_5IO_2 & \xrightarrow[H_2O]{Ag_2O} & C_{12}H_{22}O_{11} & \xrightarrow{\text{Heat}} & 4C_3H_4O_2 \\ \beta\text{-iodopropionic} & & \text{"hydracrylic"} & & \text{acrylic} \end{array}$$ (73).

This acid was investigated by Moldenhauer, von Richter, Wichelhaus and others, including Wislicenus (74) during the 1860s, and eventually it emerged that Beilstein's hydracrylic acid was in fact a polymer of β-hydroxypropionic acid, which was actually isomeric with the lactic acids. In 1868 Wislicenus suggested that it might be identical with ethylene lactic acid, but did not have time to pursue the question experimentally (75). In fact many of his research reports of the 1860s and early 70s complain of his load of administrative work and lectures and laboratory supervisions, which kept interrupting what was in any case long-drawn-out and painstaking work (76). But when he did get a chance to do his own work in the laboratory, it was clear that the discovery of β-hydroxypropionic acid raised again the question of the identity of meat lactic acid with ethylene lactic acid, not to mention the relationships between these and the new isomer. Wislicenus spent the years 1869 to 1872 in a thorough review of all the isomers.

Hardly had he started his new series of researches when he discovered that there were in fact not two isomers of lactic acid (as predicted by theory), but three: ordinary fermentation lactic acid; ethylene lactic acid, which he equated with Beilstein's β-hydroxypropionic acid; and meat lactic acid, which differed from both. This last was optically active, with a specific rotation of 3.3° to the right, and it appeared to be a modification of ethylidene lactic acid (77).

I have said that chemists were not very interested in optical activity. Certainly this was the first time that Wislicenus had mentioned the phenomenon in print. In several mentions of tartaric acid over the years, he had never remarked on this well-known property. So quite how he came to notice the phenomenon in meat lactic acid is unclear, especially since the specific rotation is so small; certainly he says nothing about the process of his discovery. But unlike other chemists Wislicenus clearly accepted optical activity immediately as a characteristic for differentiating between isomers, and was prepared to draw far-reaching conclusions from the existence of three isomers of lactic acid. In the words of Kekulé, who sent to the *Berichte* an account of the Innsbruck meeting of the Association of German Scientists in September 1869:

> The speaker drew our attention to the fact that the existence of three [hydr]oxypropionic acids demonstrated the limitations of the structural formulae in general use, as also of the views that are usually expressed in these formulae. Such

> subtler cases of isomerism might perhaps be explained by spatial presentation of the combinations of atoms, that is, by models. (78).

We have seen that Wislicenus was thinking in spatial terms from at least 1863, so these remarks need not surprise us. And we should be careful to realize that his ideas about atoms in space were fundamentally different from van't Hoff's later views. This is fully brought out by a report of a seminar in Zürich two months later, when he discussed the same topic:

> Facts such as these force us to explain the difference between two isomeric molecules which have the same structure by means of different arrangements of their atoms in space... Possibly an exact determination of the densities of the modifications of lactic acid will reveal a difference in the space occupied by the molecules. Perhaps optically active meat lactic acid... does not have its atoms arranged together in the smallest possible space. (79).

This difference in density is a far cry from van't Hoff's geometrical arrangement of atoms in three dimensions, though both could broadly be referred to as "the arrangement of atoms in space". Wislicenus pursued these hypothetical speculations to the extent of carrying out density measurements (80). These were presumably inconclusive, for he never published any results.

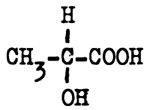
Meanwhile he pursued his thorough chemical investigation of all the lactic isomers. He next discovered that meat lactic acid was a mixture, rather than a pure substance (81). The major component was the optically active ethylidene lactic acid - or paralactic acid, to use the term that Wislicenus definitively adopted from Heintz in 1873 (82) - while ethylene lactic acid also occurred in meat in varying proportions, and the two were always obtained together; in some pathological conditions, ethylene lactic acid was found free of paralactic acid (83).

Rather more important, when he further investigated Beilstein's β-hydroxypropionic acid - or hydracrylic acid, as he now called it (84) - he concluded that it was not identical with ethylene lactic acid, as he had thought in 1869, but a distinct acid (85). This raised further problems for chemical theory, for there were now not three isomers where only two were predicted by theory, but four; and further to complicate matters, the four isomers could be grouped into two pairs, but the relationship between the two members of each pair was by no means the same.

Rather than discussing in confusing detail Wislicenus' summary of the position in 1873, which runs to 116 pages in the Annalen, and is full of experimental and theoretical arguments, let me briefly sketch what was then known to Wislicenus about the various isomers. (see the Table on the next page).

1. There was very little doubt about the nature of ordinary lactic acid, or about its formula based on the ethylidene radical.
2. Wislicenus regarded paralactic acid as a modification of the ordinary acid. Its chemical behaviour was broadly the same, and

ISOMERS OF LACTIC ACID KNOWN IN 1873

	NAME(S)	MODERN NAME	DATE	FORMULA	SOURCES
1.	Milk lactic acid Fermentation lactic acid Ethylidene lactic acid α-hydroxypropionic acid	DL-lactic acid	1780	 $CH_3-\overset{H}{\underset{OH}{C}}-COOH$	Fermentation of carbohydrates Synth. from acetaldehyde propylene glycol
*2.	Meat lactic acid Paralactic acid Sarcolactic acid	L(+)-lactic acid	1848	Same as (1)? [dextrorotatory]	Meat extract
3.	Ethylene lactic acid	Hydracrylic acid	1862	$HO-CH_2-CH_2-COOH$	Meat extract Synth. from ethylene cyanohydrin
4.	Hydracrylic acid β-hydroxypropionic acid	Hydracrylic acid	1864	? ?	Synth. from β-iodopropionic acid

Source: Wislicenus (86).

* Unknown to Wislicenus (or at least unappreciated by him), the laevo-form had probably also been obtained at this time. Messrs. T. and H. Smith, morphine manufacturers, of London, had obtained a lactic acid from the mother-liquor of macerated opium. The morphine salt (and some other salts) of this acid differed from the ordinary lactates, so they considered it a special modification, and called it "thebolactic acid" (87). In view of the fact that J. C. Irvine discovered in 1906 that morphine laevolactate crystallized readily from aqueous solution, while the dextrolactate was extremely soluble, and only crystallized after standing for several weeks in a vacuum dessicator (88), it is very probable that many samples of thebolactic acid were at least richer in the laevo-form. However, J. Y. Buchanan examined one sample from Smiths' in 1870 and considered it to be the ordinary inactive acid (89).

If I am right in thinking that thebolactic acid was at least slightly laevorotatory, then the appropriate entry in the above table would be:

2b.	Thebolactic acid	D(-)-lactic acid	1862	Same as (1)? [laevorotatory]	Macerated opium mother-liquor

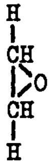
In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

in particular he was impressed by Strecker's demonstration (90) that paralactic acid could very simply be converted into ordinary acid. The chief distinguishing characteristic was the optical activity of paralactic acid, though there were also some differences in the solubility and the water of crystallization of the respective salts (91). Most chemists, however, still interpreted the differences in terms of polymerization: ordinary lactic acid was regarded as the dimer of paralactic acid.

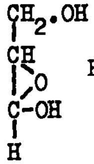
3. Wislicenus had synthesized ethylene lactic acid in 1862, and had based its formula on the ethylene radical. He had later identified it as the minor component of so-called sarcolactic acid from meat extract, though Erlenmeyer (92) had disputed this finding.

4. There was a considerable problem about the relationship between ethylene lactic and hydracrylic acids: since both contained no methyl group, but rather the $-CH_2OH$ group, they were clearly similar (93); on the other hand, there were enough distinct differences so that this could not be another case of two bodies having the same structural formula - they could not be mere "geometrical" isomers (94). In particular, ethylene lactic acid gave malonic acid on oxidation and hydracrylic acid did not; zinc ethylene lactate crystallized easily, but not zinc hydracrylate; most important, ethylene lactic acid neither gave β-iodopropionic acid by the action of hydrogen iodide, nor formed an insoluble zinc-calcium double salt, both of which were essential characteristics of hydracrylic acid (95).

If the possiblilities of the conventional structure theory were exhausted by the formulae for ethylidene and ethylene lactic acids, and ethylene lactic and hydracrylic acids were not geometrical isomers with the same structural formula, then what possibilities remained? Wislicenus was able to use a different structural formula for hydracrylic acid which contained an oxiran ring, and which was perhaps inspired by the current formula for ethylene oxide:

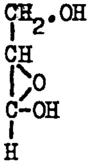


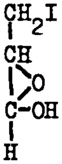
Ethylene oxide

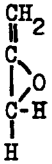


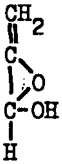
Hydracrylic acid (96).

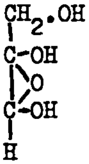
(The decision to assign the ordinary linear formula to ethylene lactic acid, and the ring formula to hydracrylic acid, was due to Wislicenus' having originally prepared ethylene lactic acid from ethylene cyanohydrin.) The arguments supporting this rather unlikely-looking ring structure are complex, and have to do with the nature of several allied compounds, but are ultimately based on the formation of crotonaldehyde from acetaldehyde (97), which of course involves a rearrangement during the aldol condensation that Wislicenus could not have suspected. This revision of the hydracrylic acid structure naturally involved a similar revision for many other compounds, which if pursued would have led to extreme complications:


Hydracrylic acid


β-iodopropionic acid


Acrolein

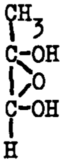

Acrylic acid


Glyceric acid

This type of oxiran ring formulation was supported by other chemists, such as Erlenmeyer (98). It is of course the only way in which the current structural theory could be extended to cover more than two isomers of lactic acid without going into three dimensions, and arrangement in space (99).

But the relationship between ordinary lactic acid and paralactic acid was different in kind from that between ethylene lactic and hydracrylic acids, so it was not possible to explain the former case of isomerism by juggling with structural formulae in this way. Wislicenus did mention a formula for paralactic acid containing an oxiran ring:


Hydracrylic acid


Paralactic acid?

but he immediately dismissed it as impossible, because this formula would imply that hydracrylic acid, too, should be optically active, which was not the case (100).

So if Wislicenus had not been concerned with what we now know to be a false distinction between hydracrylic and ethylene lactic acids, it would have been quite possible for him to have used an oxiran formula for paralactic acid, and he might not have been forced into a consideration of the arrangement of atoms in space; as it was, there was absolutely no alternative. This brings us back to our starting point, and van't Hoff's immediate inspiration.

Wislicenus and van't Hoff

I have traced how Wislicenus was forced to the conclusion that the structural theory broke down in the case of the lactic acid isomers; this side of the story is comparatively well known. But the simple theoretical picture was vastly complicated by practical difficulties (and this was indeed the case with the study of lactic acid throughout the century). Wislicenus got himself trapped in an experimental dead end as well as a theoretical dead end.

What is one to make of Wislicenus' experimental failure? Clearly some practical techniques were not as secure around 1870 as might be imagined. In particular, Wislicenus was obviously unable to purify his lactic acids properly; I have already mentioned my suspicion that virtually every sample he examined was more or less a mixture. "Ethylene lactic acid", for instance, must have been a mixture of ordinary lactic and hydracrylic acids. In 1873 Wislicenus admitted that after years of trying, he had finally given up all hope of preparing a pure sample of ethylene lactic acid (101), and he talked of 'the well known impossibility of purifying completely bodies which are extremely soluble, which do not crystallize, and which cannot be distilled' (102). Unfortunately, those properties which Wislicenus relied on most for distinguishing between isomers - solubility, the appearance of crystals, the percentage of water of crystallization, the melting point, the action of heat - are of course precisely those which are most upset by the presence of impurities.

We must remember that Wislicenus was not alone in seeing isomerism where we see only identity; adherents of both the type theory and the radical theory considered methyl-propyl to be an isomer of diethyl, though we would call them both butane. The work of Wurtz and, more important, Schorlemmer (103) only slowly succeeded in discrediting this view, which was still widely current in the late 1860s and early 70s. And in 1869 Paternò believed that there were three isomers of dibromoethane, and proposed a tetrahedral model to get round the limitation of the structural theory which could not explain these (104). Once mythical isomers had got into the literature, either for theoretical reasons, as for the paraffins, or for practical reasons in the case of dibromoethane or ethylene lactic and hydracrylic acids, then it was very difficult to get rid of them; the determination of chemical properties and, perhaps more important, of physical constants, was not yet sufficiently reliable.

That Wislicenus was not simply a poor experimentalist is shown by the delicate and splendid work he later did in resolving geometrical isomers, when the theoretical and experimental way was clear to him. In his examination of the lactic acids, though, he was floundering. Because a certain amount of his data was inaccurate, his account does not hang together logically; he appears to be going round in circles. His voluminous arguments make heavy reading, as van't Hoff found at the time, and later recalled:

> Students, let me give you a receipe for making discoveries. In connexion with what has just been said about libraries, I might remark that they have always had a mind-deadening effect on me. When Wislicenus' paper on lactic acid appeared and I was studying it in the Utrecht library, I therefore broke off my study half-way through, to go for a walk; and it was during this walk, under the influence of the fresh air, that the idea of the asymmetric carbon atom first struck me. (105).

van't Hoff's hypothesis certainly came as a breath of fresh air to Wislicenus, who when it appeared had been struggling with the problem of the lactic acid isomers for about five years. No wonder that he was the first chemist to welcome it enthusiastically (106), or that he sponsored the German translation that made it widely known, or that he was the first to make significant further use of the hypothesis, in the work on geometrical isomers mentioned above.

As for ethylene lactic acid, neither van't Hoff nor Le Bel mentioned its isomerism with hydracrylic acid, and though Wislicenus was still discussing it in 1875 (107), he turned his attention to other things thereafter, and ethylene lactic acid disappeared from the chemical vocabulary. It had served its purpose.

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19. See the indexes to Annalen during the nineteenth century. After regular and frequent mentions between 1832 and 1873, lactic acid ceased to be of interest to chemists thereafter.
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30. Pelouze, T.J., J. de Pharm. (1845) 7, 5-15.
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34. ibid., 328-31.
35. Engelhardt, H., Annalen (1848) 65, 359-67 (363). My schematization.
36. ibid., 359
37. See for example A.F.L.Strecker, Annalen (1854) 91, 352-67.
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39. Strecker, A.F.L., Annalen (1850) 75, 27-45.
40. See Russell, C.A., "The history of valency", pp.21-80; Leic-

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41. Wurtz, C.A., Comptes Rendus (1858) 46, 1228-32.
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45. Perkin, W.H. (Senr.), Chem. News (1861) 3, 81-3.
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47. In a tantalizing footnote to the above quotation (p.174n) Kekulé says: 'If the constitution of glycollic acid is represented by the graphical method of schematization already used [his "sausage formulae"], the asymmetrical constitution of glycollic acid, and the dissimilar arrangement of the hydrogen atoms, emerge particularly clearly'. Unfortunately, Kekulé did not himself follow this suggestion, at least in print; but A.Crum Brown did so in his M.D. thesis of 1861 (publ. Edinburgh, 1879), p.23.
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49. ibid., 113-4, and passim.
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56. ibid., 77.
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59. see note 39.
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73. Beilstein, F.K., Annalen (1862) 122, 366-74.
74. For references see J.Wislicenus, Annalen (1873) 166, 3-64 (6-8).
75. Wislicenus, J., Tageblatt der 42 Versammlung deutscher Naturforscher und Aertze in Dresden (1868), p.184.
76. See for instance J.Wislicenus, op. cit. (74), 3-4.
77. Wislicenus, J., Tageblatt der 43 Versammlung deutscher Naturforscher und Aertze in Innsbruck (1869), p.65; see also the report of this meeting by A.Kekulé, Ber. (1869) 2, 550-1. The association of this meat lactic acid with ethylidene lactic acid was due to Strecker's demonstration of their interconvertibility (see note 51); see O.Meister, op. cit. (18), 621.
78. Kekulé, A., op. cit. (77), 551.
79. Meister, O., op. cit. (18), 620-1.
80. Wislicenus, J., Annalen (1873) 167, 302-46 (304).
81. Meister, O., op. cit. (18), 620.
82. Wislicenus, J., op. cit. (80), 304.
83. Kekulé, A., op. cit. (77), 550; Meister, O., op. cit. (18), 620.
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343-6.

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93. Wislicenus, J., op. cit. (74), 45, 47.

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99. See Benfey, O.T., J. Chem. Educ. (1957) 34, 286-8.

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103. Wurtz, C.A., Ann. Chim. (1855) 44, 275-313; Schorlemmer, C., J. Chem. Soc. (1864) 17, 262-5, and Phil. Trans. Roy. Soc. London (1872) 162, 111-23. See C.A.Russell, op. cit. (40), 155, for a discussion of how slowly Schorlemmer's evidence was accepted. Frankland, who had done as much work on the paraffins as anyone (except Schorlemmer) remained sceptical as late as 1877.

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106. Wislicenus, J., op. cit. (69). See also the personal letter from Wislicenus to van't Hoff of 10 November 1875, reproduced in E.J.Cohen, op. cit. (3), 114.

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4

Practical and Theoretical Objections to J. H. van't Hoff's 1874-Stereochemical Ideas

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On September 5, 1874, the Dutch chemist Johannes Henricus van't Hoff published in Dutch a pamphlet, entitled: "Proposal for the extension of the structural formulae now in use in chemistry into space, together with a related note on the relation between the optical active power and the chemical constitution of organic compounds". Starting with the ideas of August Kekulé on the quadrivalency of carbon, combined with the concept that carbon atoms can combine directly with one another to form chains of any length and complexity (1858), and with the three articles on lactic acids written by Johannes Wislicenus (1873), van 't Hoff supposed that the four affinities of a carbon atom are directed to the corners of a tetrahedron with the carbon atom at the center. Introducing the concept of the asymmetric carbon atom as an atom "combined with four univalent groups", van't Hoff could gave a satisfying explanation of numerous cases of optical active isomers. Further it appeared that compounds containing doubly and triply linked carbon atoms are also a corollary of the concept of the tetrahedral carbon atom.

The ideas which van't Hoff published in his"Proposal" attracted but few attention in the chemical world. This did not change after the publication of the French translation or when an extended version had appeared in 1875 as "La Chimie dans l'Espace" (1). The revolutionary ideas of the young Dutch chemist aroused interest only after when a pupil of Wislicenus, Felix Hermann(1877) had made a German translation of his booklet (2). Yet van't Hoff had made enough publicity for his ideas. He had sent copies of "La Chimie dans l'Espace" with a collection of tetrahedral cardboard models to a number of well-known chemists. He got warm acknowledgments from Walther Spring, Adolphe Wurtz, and Louis Henry. Adolph von Baeyer found the theory "a new good thought in our science, which will bear ripe fruits" (3). But in fact only Wislicenus was very enthusiastic.

In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

Although Hans Landolt stated in 1877 that there are no examples opposed to the theory of van't Hoff (4), most chemists were critical of it. However the well-known attack of Hermann Kolbe was no serious criticism. He held firmly to the belief that the arrangement of atoms in a molecule was unknowable and he considered every attempt to give a chemical structure as "pictures of imagination". In 1877 he gave as one of the reasons for the - to his view - decline of chemical research in Germany "the lack of well-rounded as well as thorough chemical education." He noticed in the backward trend of German chemical research the regeneration of "the seemingly learned and ingenious but in reality trivial and stupefying Naturphilosophie" (5). As an example he mentionned van't Hoff's "Die Lagerung der Atome im Raum". He thought it impossible to review this book in any detail "because the fancy triffles in it are totally devoid of any factual reality and are completely incomprehensible to any clear-minded researcher":

A Dr. J.H. van't Hoff, of the Veterinary School at Utrecht, finds as it seems, no taste for exact chemical research. He has thought it more convenient to mount Pegasus (obviously loaned by the Veterinary School) and to proclaim in his "La Chimie dans l'Espace" how during his bold flight to the top of the chemical Parnassus, the atoms appeared to him to have grouped themselves troughout universal space.

Ten years later van't Hoff remarked that "at the present moment this opposition has disappeared in Germany with the death of Kolbe, and is now only sustained in France in the person of Berthelot" (6).

Practical Objections Against van't Hoff's Ideas

In the meeting which the "Société Chimique de Paris" held on March 19, 1875, Arthur Rodolphe Marie Henninger communicated on behalf of his friend van't Hoff "a theoretical work on the structural formulae into space". The nestor of the French chemists Marcellin Berthelot criticized the stereochemical ideas of the young Dutch chemist. First of all he objected to the fact that van't Hoff did not take into account the "rotatory and vibratory movements by which are 'animated' every atom in particular and every group of atoms in the molecule" (7). More important were Berthelot's practical objections. He referred to the researches of Louis Pasteur, who had found four forms of tartaric acid: the D- and the L-forms, a racemic form(which is optically inactive because of equal proportions of the D- and L-forms), and a meso form (a truly inactive form of the acid as the consequence of internal compensation). However Pasteur stated that he had also found four forms of malic acid (8). Starting from the inactive aspartic acid made by Victor Dessaignes by heating acid ammonium fumarate (9) he had obtained an inactive malic acid which could not be resolved into the optically active forms. This meso type was, indeed, not explainable with van't Hoff's theory because the constitutional formula of malic acid contains only one asymmetric carbon atom. So the objection of Berthelot was justified. A number of chemists assumed the existence of this inactive, indivisible type as quite general (10). The difficulty was removed after the experiments of Bremer, Anschütz, and H.J. van't Hoff, who proved that all the malic acids obtained by the different methods known at that time, has been identified with the inactive acid obtained by mixing equal quantities of the D- and L-acids and all have been separated.

Gustav Jacob Wilhelm Bremer was the first Netherlander who used the theory of his college friend van't Hoff. He did this in his thesis on "a dextro-rotatory malic acid" (October 15, 1875) (11). Bremer prepared a real D-malic acid, enantiomorphous with the L-acid, by partial reduction of D-tartaric acid with a mixture of iodine, phosphorus, and water. From his experiments he concluded that D-tartaric acid gives D-malic acid, but that racemic acid gives inactive malic acid. However he discovered that the specific rotatory power of the acid ammonia salt of malic acid prepared from tartaric acid was not the same as the value for the acid ammonia salt of malic acid obtained from mountain-ash berries (resp.+ 7°,912 and - 5°,939) (12). Why do not both salts possess equal and contrary values like the salts of D- and L-tartaric acid ? The solution of the problem was given by van't Hoff. With a letter (13) on July 13, 1875, he sent Bremer a set of his tetrahedron models, which are now at the Leyden Museum. With these models he explained the optical activity of malic acid and tartaric acid. Now Bremer was able to solve the apparent anomaly in the rotation powers of the acid ammonia salts of malic acid. He said:

> One must take into consideration that, when the malic acids possess equal, but contrary rotation powers, their salts may have different ones (14).

It is true that the two salts are isomers, but not in the sense of the stereo-isomers of van't Hoff. In a letter of October 1875, van't Hoff wrote to Bremer that the observations of the latter on the rotatory power of the malic acids are in agreement with his theory:

> Apparently contrary to your result, apparently, because your determinations are done with the acid ammonia salt and it is clear that each of the malic acids predicts two acid ammonia salts:

$CO_2H.\underline{C}H(OH).CH_2.CH_2NH_4$ (a)

and $CO_2NH_4.\underline{C}H(OH).CH_2.CO_2H$ (b)

Now it is conceivable, that one of the acids gives an ammonia salt (a), the other (b), and then of course the prediction of equal and contrary activity disappeared, because then the surrounding groupings are no more the same, but in the case of

a	b
CO_2H	CO_2NH_4
$H.OH$	$H.OH$
$CH_2(CO_2NH_4)$	$CH_2(CO_2H)$

At the advice of Eduard Mulder, the preceptor of both Bremer and van't Hoff, Bremer later separated the inactive malic acid by the alkaloid cinchonine (15).

Another Netherlander who studied the malic acids was the younger brother of van't Hoff, Herminus Johannes (16). In his thesis on the malic acids he proved the identity of the inactive malic acid obtained from aspartic acid(Pasteur) monosuccinic acid and silver oxide (Kekulé), and fumaric acid and caustic soda (Loydl). He showed that they are all identical with Bremer's acid as follows from a study of the crystal forms of the acid ammonia salts. Because Bremer succeeded in separating his malic acid by the alkaloid cinchonine, this holds for all so-called inactive inseparable malic acids.

Another problem was the statement of Pasteur that there exists an optically active succinic acid (17), which Kekulé tried unsuccesfully to prepare by the reduction of the inactive malic acid (18). van't Hoff stated that the succinic acid does not have an asymmetric carbon atom, and therefore it cannot have an optically active form. Together with Bremer he studied the succinic acid (19), which the latter had obtained during his reduction experiments. They found no activity in succinic acid and they showed the relationship: D-tartaric acid (with two asymmetric carbon atoms) yields on reduction D-malic acid (with one asymmetric carbon atom) and this yields succinic acid (with no asymmetric carbon atom).

Besides the malic and the succinic acids (20) two other organic substances were known in 1874 which were found to be active: propyl alcohol and styrene. In the "Proposal" van't Hoff mentionned that the only exception to his rule that "every compound of carbon which in solution rotates the plane of polarized light possess an asymmetric carbon atom" was propyl alcohol, reported to be active by the French chemist Gustav Chancell (21). However Henninger wrote him that the relative small rotatory power of this compound was due to the presence of an impurity, viz. amyl alcohol (22).

More problems gave Berthelot's claim that styrene obtained from storax is optically active (23). Like propyl alcohol, styrene has no asymmetric carbon atom. van't Hoff repeated the experiments of Berthelot and was able to show that the rotatory power of styrene is due to the presence of an active body of different composition (24). He supposed that the liquid oil obtained by the distillation of storax (a semi-solid balsam containing cinnamyl cinnamate, which in distillation gives styrene as a volatile oil) is a mixture because the specific rotatory power of the liquid oil is not a constant one but depends on the experimental conditions. Further, according to a quantitative organic analysis, the oil seems composed of 79,56 per cent carbon and 9,91 per cent hydrogen, while the theoretical values for styrene (C_8H_8) are 92,31 per cent carbon and 7,69 per cent hydrogen. van't Hoff distilled the liquid oil at the boiling point of styrene, which polymerizes to a glassy substance, metastyrene $(C_8H_8)_n$. The liquid collected in the receiver had a higher rotatory power, the value of which agrees with that calculated from the original styrene. In the first distillation 25 grams of the original styrene (rotating at - 5°,543) gave on distillation above 130°C a residue of metastyrene, and in the receiver 16,6 grams of a liquid rotating at - 8°,36. (Calculated from the original styrene the rotatory power of the liquid was - 5,54 x 25/16,6 = - 8°,342). In a second distillation 16,4 grams of the liquid rotating - 8°,36 gave 5,5 grams of metastyrene, and in the receiver a liquid rotating - 12°,67 (calculated from the styrene distilled -12°,58). A third distillation gave after five hours heating at the boiling point besides metastyrene a liquid entirely different from styrene both in composition and in properties: it had a boiling point of 170-180°C, was laevo-rotatory, contained oxygen, and possessed lesser carbon but more hydrogen than styrene. van't Hoff thought that the formula was not far removed from $C_{10}H_{16}O$, and he called it "styro-kamfer".

However, Berthelot adhered to his original opinion. He repeated his experiments, got the same results, but made no quantitative analysis as van't Hoff had done. He came to the conclusion that "the optical rotatory power of styrene is certain, and with that every theory which is incompatible with this property is convicted of inaccuracy" (25). Now van't Hoff studied the optical activity of pure metastyrene and of styrene derivatives (26). He prepared crude styrene by distillation of storax. Treatment with a solution of caustic potash and with ether gave a D-rotatory substance. He saponified it with caustic potash, and after precipitating it with water, he obtained crude cinnamic alcohol. In the crude alcohol there were three substances, all inactive: cinnamic alcohol, benzyl alcohol, and phenyl propyl alcohol. From this van't Hoff came to the conclusion that in the mixture there was still another, optically active substance which was probably identical with the alcohol $C_{10}H_{18}O$, which Wilhelm von Miller obtained by the slow distillation of cinnamic acid (27).

Theoretical Objections Against van't Hoff's Ideas

Most chemists in the 1874's were sceptical of van't Hoff's ideas because they did not agree that he started from the physical reality of atoms and molecules. Further a number of chemists (like Rudolf Fittig, Alexander Claus, Wilhelm Lossen, Friedrich Hinrichsen) were convinced that the theory was incompatible with physical laws. For Le Bel's abstract geometrical ideas there was scarcely any criticism, because he did not started from any atomic model.

In the nineteenth century most chemists considered the atomic theory as an interesting and handy theory. However about the existence of such smallest particles as a reality there could nothing be said with certainty. The atomic theory was accepted as a mathematical theory, which does not need to be true to Nature, but is useful for calculation and systematization. Only in 1843 Leopold Gmelin "definitely went over to the atomic hypothesis" (28), but Justus Liebig denied in 1844 the existence of particles of matter which are absolutely indivisible (29). Most chemists and physicists granted that they used the atomic theory as an expedient for the explanation of natural phenomena (30). Kekulé, who exerted a great influence on van't Hoff, stated in 1867:

> The question whether atoms exist or not has but little significance in a chemical point of view: its discussion belongs rather to metaphysics. In chemistry we have only to decide whether the assumption of atoms is an hypothesis adapted to the explanation of chemical phenomena (31)

From a philosophical point of view Kekulé "did not believe in the actual existence of atoms, taking the word in its literal signification of indivisible particles of matter". As a chemist he regarded "the assumption of atoms, not only as advisible, but as absolutely necessary in chemistry". As a number of his fellow-chemists he made a distinction between chemical and physical atoms. He believed in chemical atoms, that is "those particles of matter which undergo no further division in chemical metamorphoses", but about physical atoms, the indivisible particles of matter, nothing can be said with certainty.

In the Netherlands the situation was not different (32). Petrus van Kerckhoff found the atomic theory "a remainder of the a priori study of Nature which sometime ago was in general use" (33). It cannot abide the test of a sound criticism which considers experience as the only source of real knowledge. We do not know how a chemical combination originates, how the components are in it. It is better to confess frankly our ignorance than to indulge in imagined knowledge. Therefore he rejected the "atomic opinion". In his inaugural oration at Utrecht (1868), he objected against the explanation of isomerism and allotropism by means of a different position of atoms into space. That is a problem which is "at this moment inaccessible to chemical investigation" (34). Van Kerckhoff's colleague Eduard Mulder was also sceptical about the atomic concept (35), so that it is not strange that he was not enthusiastic about the ideas of his student van't Hoff. An entirely different attitude had Jan Willem Gunning, since 1865 professor at Amsterdam, who stated in 1873 that the atoms "are the last, real elemental components of the substances" (36). van't Hoff knew Gunning very well and it is not surprising that the latter was immediately enthusiastic about the concepts as given in the "Proposal".

van't Hoff accepted without comments the physical reality of the existence of atoms and molecules. He started his book "Ansichten über die organische Chemie" (1878) with the statement:"Chemistry is the doctrine of atoms; organic chemistry that of the carbon atom" (37). The fundamental idea underlying his work was that "the molecule is a stable system of material points" (38). He understood clearly that if we are superimposing three-dimensional formulae upon their mirror-image we have in fact accepted the reality of these formulae:

> When we arrive at a system of atomic mechanics the molecule will appear as a stable system of material points; that is the fundamental idea which continually becomes clearer and clearer when one is dealing with stereochemistry for what we are dealing with here is nothing else than the spatial - i.e. the real - positions of these points, the atoms (39).

He also cleared up the repeated objections to the tetrahedral theory on the basis of the kinetic theory of matter for reconciliation of that theory with the static role required of the atoms in van't Hoff's theory. Indeed in the latter it is accepted implicitly that the atoms or radicals which are in the corners of a tetrahedron have fixed positions. The first chapter of "La Chimie dans l'Espace" begins with the sentence:

> Modern chemical theory has two weak points. It expresses itself neither as to the relative position of the atom in the molecule nor as to their movement (40).

In his theory van't Hoff confined his attention almost exclusively to the question of the relative position. Incidentally however the movements of the atoms also have been considered. Therefore he suggested that the atoms probably oscillated rapidly about their mean positions in the molecule (intramolecular atomic movement). He wrote:

> We have the molecule, a combination in which the four affinities of the carbon are satisfied by four univalent groups,considered as a general stable system of five mass points. The intramolecular movements, which must be simply accepted according the state of modern science, can consist in oscillation of the atoms round certain equilibrium states, from which follows that the relative stability of the system undergoes no change (41).

Although Wislicenus could said in 1894 that "the old opposition to the principle has almost died out; where it still lives it is directed against the ultimate basis - against the Atomic Hypothesis itself - and does not deny that the doctrine of atomic arrangement in three dimensions is a logical and necessary stage, perhaps the final stage, in the chemical theory of atoms" (42), a number of chemists remained critical of the tetrahedral theory as incompatible with physical laws. Indeed van't Hoff's postulate that the four bonds of a carbon atom are directed a priori to the corners of a regular tetrahedron was contradictory to the Newtonian physics of his time, because this asserted that the direction of an attractive force is determined by the position of attracted bodies and that it cannot have a direction independent of the position of the attracted bodies. Chemists like Adolph Claus and Wilhelm Lossen opposed not only the tetrahedral disposition of valencies, but also the assumption that the valency of a polyvalent atom like carbon should be regarded as a single force which is divided a priori in several parts in the atom (43). van 't Hoff considered the carbon atom implicitly as a material point from which four forces are directed symmetrically. To solve the conflict between the physical theory and the stereochemical concepts, a number of chemists gave models about the shape of the carbon atom (44). So Aemilius Wunderlich emphasized the extensiveness of the carbon atom, the shape of it is the cause of several points of maximum attraction. Others tried to construct theories which are free from the hypothesis that there are directed forces in the carbon atom. Le Bel (45) admitted that each atom is surrounded by a spherical zone of repulsion. When the zones of repulsion of the atoms forming a molecule come into contact with each other, equilibrium is reached.

However the sceptical attitude towards van't Hoff's stereochemical ideas disappeared thanks to its elucidation and extension to a great number of examples. As Wislicenus remarked in 1894:

> For the most part the opposition is directed - often quite rightly - against special applications of the principle to the explanation of particular facts, leaving the principle itself untouched. That the hypothesis itself has proved its own justification - at least as much as any other scientific theory - none can dispute (46).

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5

J. A. Le Bel's Stereochemical Ideas Compared with Those of J. H. van't Hoff (1874)

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Two months after Jacobus Henricus van't Hoff (1852 - 1911) published his "Proposal for the extension of the structural formulae now in use in chemistry into space, together with a related note on the relation between the optical active power and the chemical constitution of organic compounds" (Utrecht, September 5, 1874), Joseph Achille Le Bel (1857 - 1930) published his article "On the relations which exist between the atomic formulae of organic compounds and the rotating power of their solutions" (November 1874) (1). Although van't Hoff was working in the laboratory of Wurtz at the time that Le Bel was an assistant there, it seems that they never discussed the tetrahedron theory. According to van't Hoff:

> That shortly before this we had been working together in Wurtz' laboratory was purely fortuitous: we had never exchanged a word about the tetrahedron there, though perhaps both of us had cherished the ideas in secret (2).

Le Bel started with the concepts of Pasteur that there is a relation between the crystalline form and optical activity. From his experiments Pasteur came to the general conclusion that when the atoms of organic compounds are asymmetrically arranged, the molecular asymmetry appears from the crystalline form exhibiting non-superposable hemihedrism (3). In his article Le Bel formulated a rule of a general character which would predict whether the solution of a substance has rotatory power or not. "Reasoning upon purely geometrical assumptions" (4), he gave two general principles ("principes généraux"), the first which is as follows:

> First general principe. Let us consider a molecule of a chemical compound having the formula MA_4; M being a simple or complex radical combined with four monovalent atoms A, capable of being replaced by substitution. Let us replace three of them by simple or complex monovalent radicals, differing from one another and not identical with

Joseph Achille Le Bel, 1857-1930

Jacobus Henricus van't Hoff, 1852-1911. (Courtesy Universiteitsmuseum, Utrecht)

M: the body will be asymmetric (5).

From this principle follows that if a body is derived from the type MA_4 by the substitution of three different atoms or radicals for A, its molecule will be asymmetric, and it will have rotatory power. Le Bel gives two exceptions on this principle: If MA_4 has a plane of symmetry containing the four atoms A, then the substitution product will be inactive; and if in $MR_1R_2R_3R_4$ the last radical is replaced by the grouping $MR_1R_2R_3$, the two equal groups of atoms obtained neutralize or increase the activity of polarized light.

In the first principle Le Bel deals with the introduction of three new radicals in MA_4. The second principle is related to the substitution of two new radicals:

Second general principle. If in our fundamental type we substitute but two radicals R and R', either symmetry or asymmetry may appear, according to the constitution of the molecule of the type MA_4. If this molecule originally has a plane of symmetry passing through the two atoms A which have been replaced by R and R', this plane will remain a plane of symmetry after the substitution; the body obtained will then be inactive (6).

After these general considerations Le Bel notices that if only one compound is formed by the substitution of one, two or even three radicals for one, two or three atoms A, that in that case:

We are obliged to admit that the four atoms of A occupy the angles of a regular tetrahedron, of which the planes of symmetry are identical with those of the whole molecule MA_4, in this case no bisubstituted compound will possess optical rotatory power (7).

Although Le Bel implies here a regular tetrahedral structure for methane, it was not his starting-point as it was to van't Hoff. The latter supposed that the affinities of the carbon atoms in organic compounds are directed to the corners of a tetrahedron with the carbon atom at the center. In such a tetrahedron one can give of compounds such as $CR_1R_2R_3R_4$ two models which are noncongruent images of each other:

When the four affinities of the carbon atom are satisfied by four univalent groups differing among themselves, two and not more than two different tetrahedrons are obtained, one of which is the reflected image of the other; they cannot be superposed; that is, we have to deal here with two structural formulae which are isomeric into space (8).

In later publications Le Bel again and again protested emphatically against those who credited him with the tetrahedron theory. Still in 1890 he wrote:

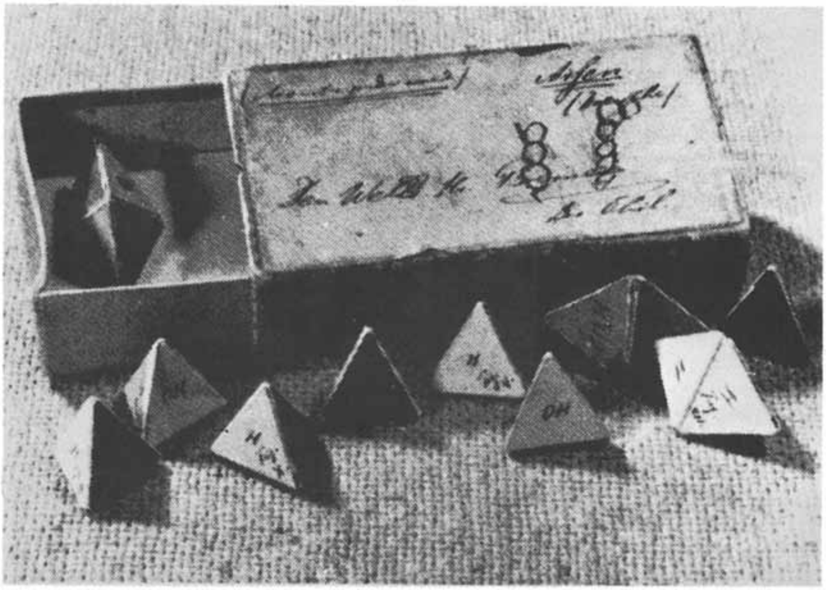
> When I published in this journal, in 1874, my article "on the relations between the rotatory power and the atomic formulae", I used the greatest efforts, in all my explanations, to abstain from basing my ideas on the preliminary hypothesis that the compounds of carbon of the formula CR_4 have the shape of a regular tetrahedron;..... it happened that a great number of scientists who wrote about my memoir most favourably in other respects, did not turn their attention to the fundamental difference, which exist between my starting-point and that of M. van't Hoff in his analogous work which he did appear at the same time in Utrecht ..... (9).

As already said Le Bel believed in Pasteur's idea that there is a direct relationship between the form of an asymmetrical substituted molecule and its crystal form. Because many molecules of the formula CR_4 crystallized in crystallographical systems other than the cubic, it seems that this was opposed to a tetrahedral configuration of such molecules. In 1892 Le Bel gave as examples carbon tetrabromide and carbon tetraiodide, which both have biaxial crystals (10).

Although Le Bel did not use structural formulae, nor the concept of valency as van't Hoff (who was guided by geometrical considerations and by Kekulé's law of the quadrivalency of carbon), his general conclusions based on pure geometrical considerations of molecular asymmetry were the same as reached by his Dutch colleague. Both introduced the idea of the asymmetrical carbon atom (by van't Hoff defined as an atom "combined with four different univalent groups" (11)) the presence of it in a molecule is the cause of molecular asymmetry and therefore of optical isomerism. However this holds only for the explanation of the optical activity in organic compounds. There is however a clear difference in the treatment of ethylene derivatives. Van't Hoff conceived a succesful model by representing two carbon atoms united by a double bond by two tetrahedrons with a common edge (12), while Le Bel distinguished two cases in the unsaturated (ethylenic) aliphatic compounds ("corps gras à deux atomicités libres") assuming that the four atoms of hydrogen (or the four radicals of a substituted ethylene) have fixed positions with regard to each other:

> If the four atoms of hydrogen lie in the same plane, which is a possible case of equilibrium, there will be no active trisubstitution derivatives; however, we do not know examples of well studies bodies derived from ethylene by three different substances, and we are therefore unable to solve this question at present (13).

The other possibility is that the four hydrogen atoms



Paper models of the asymmetric carbon atom, made by van't Hoff and sent to his friend G. J. W. Bremer on July 13, 1875. (Courtesy Rijksmuseum voor de Geschiedenis der Natuurwetenschappen, Leyden) of ethylene are not in a plane. In that case it should be possible to prepare optically active forms:

In any other case, to explain the isomerism of the ethylene derivatives, we must suppose the hydrogen atoms to be at the angles of a hemihedral quadratic pyramid superposable upon its image....., and we should obtain by two substitutions two isomers, one of which would be symmetrical, and the other asymmetrical. These isomers will both be symmetrical if the two substituted radicals are the same, as happens in the case of maleic and fumaric acids (13).

Le Bel suggested that a study of the optical properties of two substituted derivatives, such as isoamylene $CH_2= C(CH_3)C_2H_5$ and the isomeric methyl ethyl ethylene $(CH_3)CH = CH(C_2H_5)$ should decide whether the four hydrogen atoms are in the same plane or not. Here we see a basic difference between the views of Le Bel and van't Hoff. As a consequence of van't Hoff's tetrahedron theory both carbon atoms must be placed in the same plane in derivatives of ethylene. In the case of substances with two different radicals on each carbon atom (such as fumaric and maleic acids, citraconic and mesaconic acids, and so on) there exist two isomeric (cis-trans) forms. But because both isomers have a plane of symmetry neither of them is optical active. In 1875 van't Hoff referred to - then still unknown - compounds of the type $(R_1R_2)C=C=C(R_3R_4)$(14.)In these substances the radicals are in two different planes and the molecule has the shape of a sphenoid. van't Hoff predicted that, if the radicals on each carbon atom are different, optical isomerism must exist. It lasted until 1935 before Peter Maitland and William Hobson Mills discovered the optical isomeric diphenyl-di-alpha-naphtylallenes (15).

To van't Hoff optical isomerism is impossible in the case of ethylene derivatives, but Le Bel could not give a definite answer to this problem. Experiment would have to decide. First he believed that there exist optical isomers in the case of ethylene derivatives. In 1882 he accepted (influenced by the researches of Kekulé and Anschütz, who showed that oxidation of fumaric acid gave racemic tartaric acid and oxidation of maleic acid gave meso tartaric acid) that this is not the case because the molecule is plane. (16). However on February 26, 1892, the following communication was read before the "Société Chimique de Paris":

M. Lebel has looked for the separation of mesaconic and citraconic acids by means of moulds. The first gives only an inactive substance, on the other hand the fermentation products of the citraconic acid showed a strong rotatory power. The author continues his investigations (17).

Obviously Le Bel had observed that a solution of citraconic acid $CH_3C(COOH)=CH(COOH)$ acquires optical activity through the growth of fungi. Now if active citraconic acid had been formed in this way, the activity of ethylene derivatives was proved. However two years later he found that the activity was due to the formation, by addition of water, of active methyl malic acid(citramalic acid) $CH_3C(OH)(COOH)CH_2COOH$ and this no doubt accounts for the active product formed in the case of mesaconic acid also. Besides mesaconic and citraconic acids Le Bel also tried in vain to separate allyl alcohol, crotonic acid $CH_3CH=CHCOOH$ and maleic and fumaric acids. Now he came to the conclusion "that the first derivatives of ethylene are in reality planar which one had adjudged them" (18).

It is evident from the foregoing that the 1874-ideas of van't Hoff rather than those of Le Bel must considered as the foundation of the stereochemistry of organic carbon compounds.

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6

Molecular Models in the Early Development of Stereochemistry: I. The van't Hoff Model. II. The Kekulé Models and the Baeyer Strain Theory

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In the 20th Century most organic chemists find the use of molecular models, or at least perspective diagrams, almost indispensable for the discussion of a stereochemical concept. The varieties of molecular models that are available commercially or that have been prepared by individual chemists themselves attests not only to their utility but also indicates that chemists recognize that different kinds of models convey different kinds of structural and stereochemical information. A failure to appreciate this latter point will lead to an inaccurate or incomplete accounting of molecular structure and stereochemistry. That models would be useful in the illustration of stereochemical concepts was appreciated quite early in the history of stereochemistry; that the model chosen might also support a misleading or erroneous concept was not appreciated for some time however. That this is so is documented in a number of papers in this symposium volume. Some background to this paper can be found in an earlier article by the author which discusses the nature and use of models prior to about the 1860's (1).

In this paper it is intended to examine the models used in the first few decades following the publication of the papers of Le Bel and van't Hoff in 1874. The first part of the paper will be concerned with the models prepared by van't Hoff. The second part will examine the role the use of the models prepared by Kekulé had in the development and acceptance of the Baeyer Strain Theory.

Le Bel and van't Hoff. Although Le Bel and van't Hoff are both credited with the founding of stereochemistry, their initial papers published in 1874 (2, 3) differ significantly in how they approach the subject. Before discussing the van't Hoff models, some background is required concerning Le Bel. More details about Le Bel and van't Hoff are provided by Snelders in a paper included in this volume.

Le Bel's paper is not only more abstract in character than van't Hoff's but differs most notably in that it contains no diagrams or perspective formula that illustrate the stereochemical concepts.

The idea of the "tetrahedral carbon atom", which plays such an important role in the development of van't Hoff's stereochemical ideas, is mentioned only once by Le Bel and in the context of a rather general statement:

> "Let us consider a molecule of a chemical compound having the formula MA_4; M being a simple or complex radical combined with four univalent atoms A, capable of being replaced by simple or complex univalent radicals differing from one another and from M; the body obtained will be dissymetric. ...if it happens not only that a single substitution furnishes but one derivative, but also that two and even three substitutions give only one and the same chemical isomer, we are obliged to admit that the four atoms A occupy the angles of a regular tetrahedron, whose planes of symmetry are identical with those of the whole molecule MA_4; in this case also no bisubstitution product can have rotatory power." (4)

Le Bel considers that the observation of optical activity by a substance is an indication of molecular dissymmetry (in modern terminology: chirality), but that the molecular dissymmetry need not assume that the carbon valencies are directed toward the corners of a regular tetrahedron. Le Bel does appreciate that a compound having a carbon atom bound to four different groups ("simple or complex univalent radicals"), that is, an "asymmetric carbon atom", might produce a dissymmetric molecule; but at the same time, the absence of such a carbon atom would not necessarily rule out molecular dissymmetry. For example, in his discussion of the structure of ethylene, he considered that while it was possible that the four hydrogens might be coplanar, it was conceivable that the four hydrogens might be situated at the corners of a "hemihedral quadradic pyramid" (that is, a twisted prism). In the latter case it should be possible to obtain optically active unsymmetrical alkenes, such as 2-pentene. Although Le Bel was unsuccessful in several attempts to validate this hypothesis experimentally, he continued to hold the view throughout his life that the four substituents in an alkene need not be coplanar.

Although Le Bel did stimulate some stereochemical research, most notably in the resolution of tetraalkylammonium salts, he remains a somewhat obscure figure in the history of stereochemistry when compared to van't Hoff. This is not due only to the fact that many of Le Bel's ideas did not receive experimental verification, but possibly because he did not devise a means by which to impress his ideas on the minds of his contemporaries as did van't Hoff.

I. The van't Hoff Models

van't Hoff published his ideas in the Dutch language in 1874 as a short pamphlet of only 15 pages (3, 4). The last page contains 15 figures, among which 5 are perspective drawings that illustrate an enantiomeric pair for $CR_1R_2R_3R_4$, the cis/trans isomers of $R_1R_2C{=}CR_3R_4$, and an alkyne, $R_1C{\equiv}CR_2$. The pamphlet begins:

> "I desire to introduce some remarks which may lead to discussion and hope to avail myself of the discussion to give to my ideas more definiteness and breadth."

In this hope, he was apparently disappointed since his work went almost unnoticed, although a French translation was published in the same year (4, 5). In an attempt to bring his work to the attention of a wider audience, van't Hoff then prepared an expanded French edition which was published in 1875 (6). This pamphlet was 43 pages in length and includes three plates at the end which contain some 40 figures of which about half are perspective drawings. Since he felt that even on examination of the figures it still might be "difficult to follow my reasoning" he suggested that the reader refer to models constructed from cardboard. In a footnote on page 7 of the 1875 pamphlet, van't Hoff says that he will send a complete collection of the models to any reader who wishes them. He also adds that some of these models are already in the possession of a number of chemists: "Baeyer (Strasbourg), Boutlerow (St. Petersbourg), Henry (Louvain) Hofmann (Berlin), Kekulé (Bonn), Frankland (Londres), Wislicenus (Wurzbourg), Wurtz et Berthelot (Paris)." This footnote indicates that van't Hoff hoped that greater attention would be paid to his ideas if he sent the pamphlet and models to a number of prominent and influential chemists. A number of footnotes are included in the pamphlet which indicate which model numbers correspond to the figure numbers in the plates (unfortunately, the model and figure numbers are not the same).

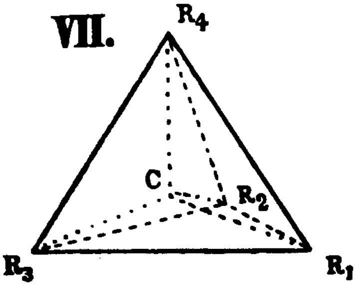
A nearly complete set of about 25 of these models have been preserved in the Deutsches Museum in Munich, Germany. These models, and the stands, (Figure 1, 2, 9, 10) were presented by van't Hoff to the museum in 1905. No correspondence or other information, other than a catalog entry, has survived concerning these models. The models, which measure about 2-2.8 cm. on edge, are displayed in two glass cases (no. 4680) titled: "Atommodelle von Prof. Dr. van't Hoff, Berlin." Figures 1, 2, 9 and 10 are black and white prints prepared from color slides and do not reveal all of the detail that might be desired. Since the Roman numerals written on the models correspond to the model numbers given in the footnotes in the 1875 pamphlet, it might be reasonably assumed that they were constructed in about 1875.

The groups bound to a tetravalent carbon atom are situated at the corners of a tetrahedron. The disposition of these groups and the carbon atom in the enantiomers of $CR_1R_2R_3R_4$ which are

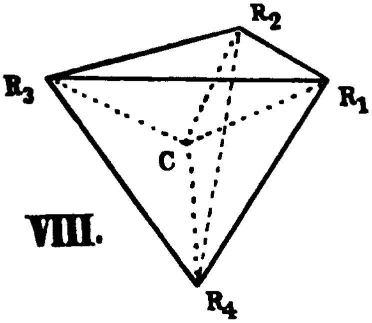
In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

illustrated in figures VII and VIII in plate 1 at the end of the pamphlet:

VII.



VIII.



Two methods were used to indicate the nature of the groups about the carbon atom in the cardboard models. In the first (which will be referred to as: Method A) the identity of the groups was indicated by letters written near the corners of the tetrahedra. The lettering can be seen in some of the 5 larger models found in the top row and right hand side of Figure 1. It should be pointed out that none of these models are constructed as regular tetrahedra. In Models XVI and XVII, which represent the enantiomers of $CR_1R_2R_3R_4$ (which correspond to figures VII, VIII in plate 1 above), all of the sides are unequal in length (varying from about 2.2 cm to 2.8 cm). In model XIII, which represents a compound having three identical groups (such as CH_3Cl), three of the edges are of the same length (ca. 2 cm.), while the fourth is longer (ca. 2.5 cm.). van't Hoff argued that a regular tetrahedron would be expected only if the four groups were identical.

In the second method of representation (method B) the different groups were indicated by coloring the faces of the tetrahedra. This method is mentioned in a second footnote in the pamplet and recommended over the first because it is easier to demonstrate, for example, the absence of isomerism in compounds that do not have four different groups. Models III and IV in the lower left-hand corner of Figure 1 represent the two enantiomers of $CR_1R_2R_3R_4$. The colors have the following correspondance: unpainted, R_1; blue, R_2; red, R_3, and yellow, R_4 (unfortunately, a black and white print can not illustrate this). The symmetry found in a molecule which contains two identical groups is apparent in model I in the upper right-hand corner of Figure 1. Two faces are unpainted, one blue, one red corresponding to the formula $C(R_1)_2R_2R_3$.

Representing the carbon-carbon single bond with the van't Hoff Models. It should be pointed out that in this method of representation, the four valency bonds from the carbon in the

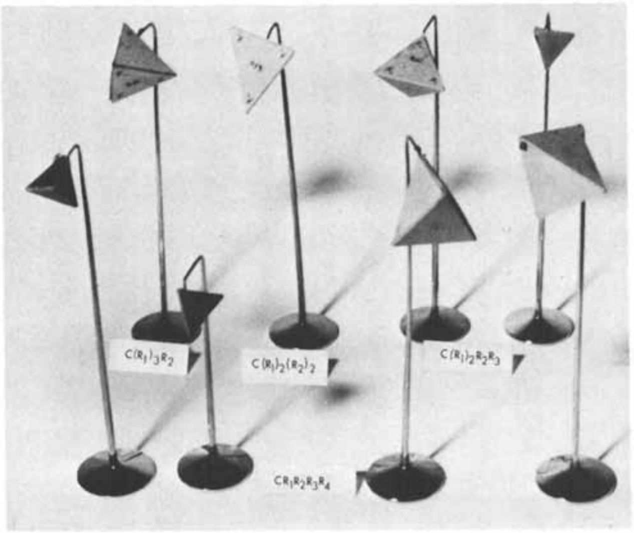


Figure 1. Cardboard tetrahedral models constructed by van't Hoff in 1877.

See *text for meanings of (A) or (B). Model numbers: Top row from left, XII(A), XIV(B), XV(A), I(B); Bottom row from left, Enantiomers III and IV(B), XVI and XVIII(A). (Courtesy Deutsches Museum, Munich)*

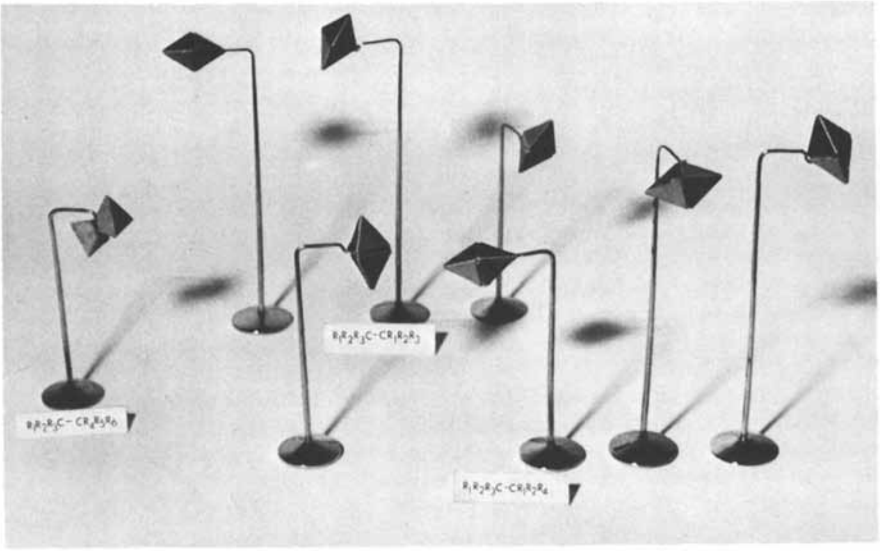
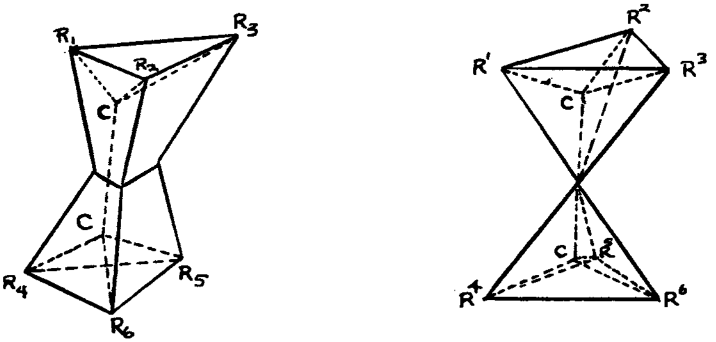


Figure 2. van't Hoff models used to illustrate stereoisomers of ethane derivatives.

Model numbers: Top row and center, VI, VII, VIII(B); far left, I(A); right bottom row: XXII–XXV(B). (Courtesy Deutsches Museum, Munich) center of the tetrahedron are directed toward the centers of the faces of the tetrahedra and not the corners, as in method A. This method finds its greatest utility in the construction of models that contain the C-C single bond.

In the first method, the carbon-carbon single bond is usually represented by the touching of the corners of two tetrahedra. In most of the diagrams that are used in stereochemistry books published in the 19th and early 20th century, this was the usual method of representation. This was the method used by van't Hoff himself in the 1877 German edition of his book(7).



1875 1877

van't Hoff's Methods of Illustrating $R_1R_2R_3C-CR_4R_5R_6$

Earlier, in 1875 he stated that ". . . it is evident that the simple union of two atoms of carbon indicated in the usual formulas by:C-C will be represented by two tetrahedra, in which the apex of one will be at the center of the other, as indicated by figure 11 [the 1875 figure above]." In 1877 the C-C bond involved only the "mutual touching of the apexes." One model (number V in Figure 2) is constructed according to the earlier view. This model shows the molecule in what we would now designate as an "eclipsed" conformation. van't Hoff pointed out that rotation about the C-C bond would produce different "phases" (different eclipsed conformations) which he represented by two-dimensional projection formula (figures XII-XVI in the first plate in the 1875 pamplet). The four possible stereoisomers (Figures 3-7) are drawings based on figures XIII-XVI in the 1875 pamplet: (Figures 18-21 in the 1877 book are similar but are not projected in the same manner).

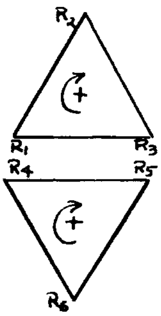


Figure 3

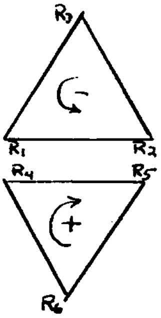


Figure 4

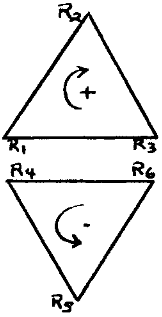


Figure 5

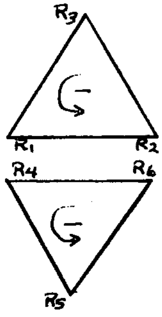


Figure 6

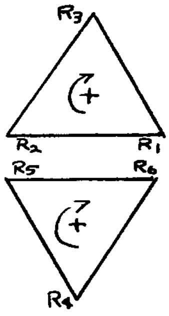
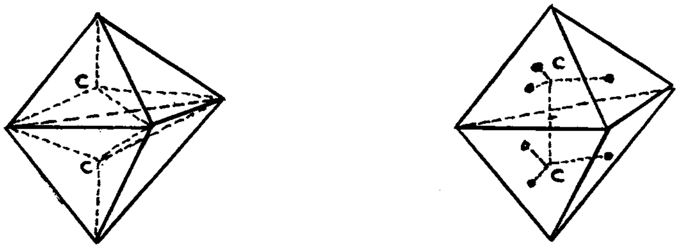


Figure 7

To generate the 2-dimensional projections from the three dimensional formula, the groups (in the 1875 formula and Figures 3-7 above) R_1, R_3, R_4, and R_5 are in the same plane; R_2 and R_6 are in another plane perpendicular to the first. Since no more than four stereoisomers of molecules whose formula corresponded to $CR_1R_2R_3CR_3R_4R_5$ were known, van't Hoff was forced to conclude that the structures illustrated Figures 3 and 7 do not represent isomeric structures"...but the same combination in two phases of a movement around the axis which unites the carbon atoms." He then went on to show how the number of possible stereoisomers is determined by the number of asymmetric carbon atoms present ($N_1=2^n$).

Thus van't Hoff has shown how models or 2-dimensional formula lead to predictions of an excess of isomers which is not supported experimentally. The lack of such isomers therefore suggests that the rotation about the C-C bonds is "free" - at least, this is how most chemists later interpreted him. In later editions of his books, van't Hoff returns to consider this problem in more detail and suggests that there may be a preferred conformation which is controlled by the nature of the groups. Under usual experimental conditions rotation about the C-C bond is permitted to allow the production of all of the possible "phases". These ideas were taken up by Wislicenus in 1887 (8) and Bischoff in 1890 (see Bykov's paper in this volume).

A model that represents the interpenetrating tetrahedra (Model I, Figure 2) is somewhat difficult to construct. If the second method of representation is used, however, the C-C bond is easily represented by the sharing of the faces of two tetrahedra (Method B, Figure 8).



$H-C{\equiv}C-H$
Method A

H_3C-CH_3
Method B

Figure 8

Methods of illustrating the carbon-carbon triple bond and single bond.

This method does not seem to have been used subsequently by other chemists probably because the models suggest the formation of a carbon-carbon triple bond (Method A, Figure 8).

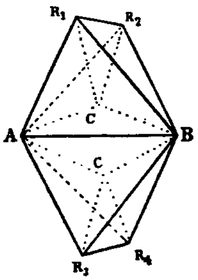
In Figure 2, models VI-VIII represent the enantiomers (VI,VII) and the meso-form (VIII) of a compound of the formula $R_1R_2R_3C-CR_1R_2R_4$. The exact correspondance of these models with the projection formula provided in the pamplet will not be discussed here.

The Ladenburg Prism Formula for Benzene. Another interesting application of the use of models is illustrated in van't Hoff's approach to the structure of benzene. In 1869, A. Ladenburg had criticized the Kekulé formula of benzene (which contained alternating double bonds) because it would predict the existence of isomeric ortho-disubstituted benzene derivatives (9). Although Kekulé attempted to answer this criticism (10) by a more "dynamic" hypothesis concerning the structure of benzene (the "oscillation" formula), Ladenburg's objection was cited for some time as the major objection to Kekulé's formula. Ladenburg had suggested a prism formula instead (9). In 1875 (6) and later in 1876 (10), van't Hoff criticized the prism formula on stereochemical grounds. With the prism formula it was also possible to have isomeric structures (that is, enantiomers) for meta-disubstituted ($C_6R_4X_2$) and ortho-disubstituted (C_6R_4XY) derivatives of benzene (Figure 9).

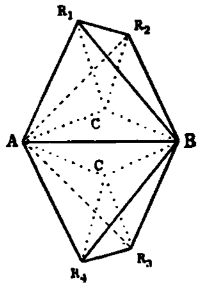
Cis/trans isomers, allene stereoisomerism. van't Hoff's use of the idea of the tetrahedral carbon atom to explain the existence of isomeric alkenes, such as fumaric acid and maleic acid, in geometrical terms was perhaps the most important extension of his theoretical ideas. Le Bel was reluctant to apply the concept of the tetrahedral carbon atom to this problem. In van't Hoff's conception, the double bond is represented by the

the sharing of the edges of two tetrahedra at A and B (Figures IX and X in the 1974 pamplet):

IX.



X.



Two geometrical arrangements were therefore possible for the molecule having the general formula $R_1R_2C{=}CR_3R_4$. It was later realized that alkenes of the formula, $R_1R_2C{=}CR_1R_2$ would also produce cis/trans isomers. The models (X and XI) which correspond to these figures (Figures XXIII and XXIV in the 1875 pamphlet) are unfortunately missing from the Munich collection. Two flat projection models (labled X_f and XI_ℓ, Figure 10) were probably used to illustrate the cis/trans isomers of $R_1R_2C{=}CR_1R_2$ (unpainted triangle, R_1; red, R_2). An unlabled model (possibly model XIX) shown in the upper left-hand corner of Figure 10 is constructed by the joining of an unlabled, regular tetrahedron on edge to an irregular tetrahedron, whose terminal apexes are labled R_1 and R_2. This corresponds to an allene of the formula, $(R)_2C{=}CR_1R_2$ (which should not exhibit cis/trans isomerism).

In 1875, van't Hoff also pointed out that optical isomerism was possible for certain compounds that contained no asymmetric carbon atoms. This was the case for allenes having the formula $R_1R_2C{=}C{=}CR_3R_4$ or other compounds containing an even number of double bonds: $(R_1R_2)C{=}C_{(2n+1)}{=}C(R_3R_4)$. The allene structure is illustrated in the 1875 pamphlet as figure XXIX. In two footnotes (P. 16,19) he points out that models XX and XXI illustrate the enantiomers of allenes having the simpler formula $(R_1R_2)C{=}C{=}C(R_1R_2)$. Only model XX (upper right-hand corner, Figure 10) has been preserved in Munich. The model is constructed by joining at two edges of an unlabled, regular tetrahedron, two irregular tetrahedra which are labled with the letters R_1 and R_2 near the terminal apexes. Since van't Hoff does not mention the allenes in the 1874 pamphlet one might assume that he stumbled upon the chirality of allenes when he began the construction of his cardboard models.

The remaining models shown in Figure 10 illustrate the possibility of cis/trans isomerism in a cyclopropane ring in which each carbon atom has two different groups (R_1,R_2). Models XXVI and XXVII (corresponding to figures XLV and XLVI in the pamplet) were constructed to illustrate these two isomers. The one model that has survived (XXVI center-top of Figure 10)

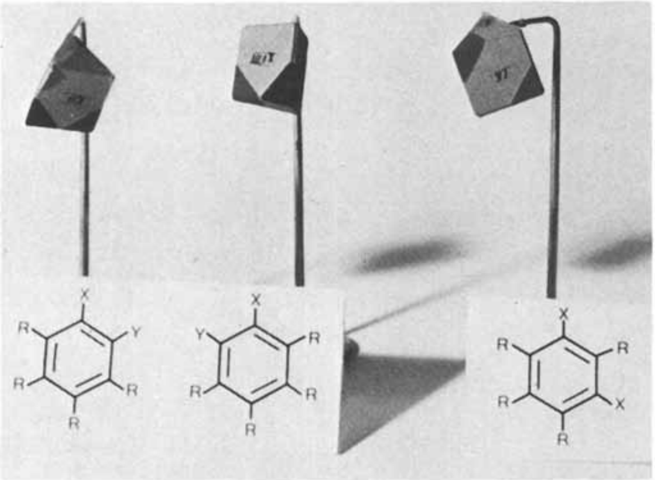


Figure 9. van't Hoff models of the Ladenburg prism formula of benzene.

Model numbers: far left, XII and XVIII are the enantiomers of o-C_6R_4XY*; IX one of the enantiomers of* m-$C_6R_4X_2$*. Corners colored: dark grey = X, black = Y. (Courtesy Deutsches Museum, Munich)*

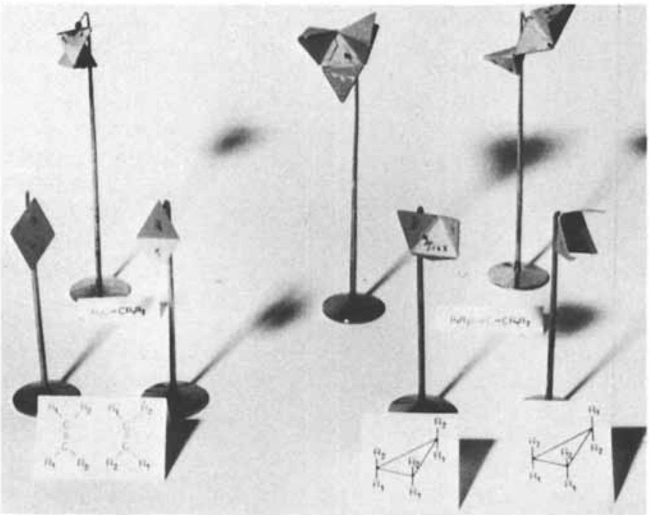


Figure 10. van't Hoff's models of alkenes, allenes, and cyclopropane derivatives.

Model numbers: top row from left, unlabeled (A), model of an alkene; XXVI(A), cyclopropane derivative; XX, allene ($R_1R_2C{=}C{=}CR_1R_2$). Bottom row: flat projection models to illustrate cis–trans isomers in alkenes and cyclopropane derivatives. (Courtesy Deutsches Museum, Munich) illustrates the cis isomer; the upper faces of the three tetrahedron are colored red and the apexes of each tetrahedron are also labeled with R_2 and R_1. The two models shown in the lower right-hand corner are constructed from single pieces of triangular cardboard which are also colored (red, R_2; colorless, R_1).

An Analogy Between Cis-trans Isomerism in Alkenes and Cyclic Compounds - A Priority Question. Thus by 1875, van't Hoff had explicitly demonstrated the analogy of the cis/trans isomerism possible for cyclopropane derivatives and the cis/trans isomerism possible for certain alkenes (maleic and fumaric acid). (The terms: "cis" and "trans" were not used by van't Hoff, however.) He suggested, therefore, that a geometrical explanation might better account for the existence of the two structures known as hydromellitic acid and isohydromellitic acid. Adolf Baeyer had earlier suggested they might be structural isomers: 1,2,3,4,5,6-cyclohexanehexacarboxylic acid and 1,1,2,3,4,5-cyclohexanehexacarboxylic acid. By the 1880's, however, Baeyer had experimentally demonstrated the existence of numerous non-structural isomers of the hexahydrobenzene di- and tri-carboxylic acids and was given the major credit by his contemporaries for the extension of the concept of cis/trans isomerism to cyclic compounds.

In 1888, F. Herrman added a footnote to a paper concerned with the stereochemistry of benzene (12) in which he expresses his opinion that van't Hoff should be given priority over Baeyer:

> "Adolf Baeyer has arrived at a geometrical configuration of the isomeric acid molecules through deliberations of a different kind. There is no doubt that these ideas of Baeyer's have been completely independently arrived at. However, I feel obliged to point out that part of his theory which will have no trouble in finding general acceptance, namely the evidence of the analogy between the two isomeric modifications of hexahydroterephthalic acid on the one hand and fumaric and maleic acid on the other, has already been given fully and clearly by van't Hoff in 1875, in the fourth chapter of 'La chimie dans l'espace', pages 40 and 41. As examples of this type of isomerism, the modifications of hexahydromellitic acid, also discovered by Baeyer, are cited here. In the German version of van't Hoff's original, in which I was given a completely free hand by the author, the chapter in question was omitted, for reasons given in the preface."

The reason given by Herrman in the preface was that he did not wish to include purely speculative discussions. Baeyer responded to Herrman's claim for van't Hoff in a footnote to a paper he published in 1890 (13):

> "Since it can be seen from these words that van't Hoff was the first to point out the similarity of the isomerism of hexahydromellitic acid with that of maleic and fumaric acid, citraconic, itaconic and mesaconic acids. With these acids

> the process is not so easy to follow as they are unsaturated making the possibilities of displacement more varied. However, the transition to normal lactic acid shown by muscle lactic acid when heated is just as simple.'
>
> I should have quoted the passage in van't Hoff's brochure given by Herrman if it had not been missing in the German edition, which was the one I happened to have available. In any case, van't Hoff's argument and diagrammatic representation are limited to describing illustrating the Kekulé model."

Baeyer's response seems somewhat ambiguous. Since van't Hoff had indicated that the models he had prepared were in Baeyer's possession by 1875, it is difficult to understand why Baeyer made no reference to them or the French pamphlet, which he presumably sent with the models. It is possible, of course, that following the publication of Herrman's German edition of van't Hoff's book in 1877 that Baeyer had discarded the French edition along with the models. By the early 1880's Baeyer was also using the Kekulé models which were more versatile in illustrating his "strain theory." Baeyer's last statement concerning van't Hoff's representation of the Kekulé model is in reference to the structure of benzene (with alternating single and double bonds). By 1888 Baeyer had adopted a "centric" formula for benzene which he illustrated with the Kekulé models (15). This formula will be discussed in Dr. Koeppel's paper in this volume. Part II of the present paper will be concerned with the further discussion of Baeyer's strain theory.

The Leyden Models. The models preserved in the Rijksmuseum voor de Geschiedenis der Natuurwetenschappen in Leyden were sent by van't Hoff along with a letter to G.J.W. Bremer on July 13, 1875. The models were used to explain the optical activity of malic acid and tartaric acid. The problem with which Bremer was concerned has already been discussed by Snelders in an earlier paper, which also contains a photograph of the models (16). The models are of about the same dimensions (1.5 cm. on edge) as the Munich models. The faces are painted different colors corresponding to different groups about the asymmetric carbon atom (white, H; yellow, OH; red, CO_2H; black, CH_2CO_2H or $CH(OH)CO_2H$). The group is also written on the face. The 10 models illustrate the enantiomers of malic acid and tartaric acid, "inactive" (meso-) tartaric acid, and succinic acid. Again the carbon-carbon bond is indicated by the sharing of the faces of two tetrahedra.

II. The Kekulé Models and the Baeyer Strain Theory

In most historical discussions of the origin and development of the Baeyer Strain Theory little attention has been paid to the kind of models used and what effect their use might have had on how the structures of cyclic compounds were perceived.

That Baeyer did not seem to have appreciated that the 6-membered ring should be multiplanar has generally been viewed as a serious error on his part and one that he could have avoided had he gone to the trouble to construct the cyclohexane ring with his tetrahedral carbon-atom models. It is the purpose of this paper to show that this represents a serious historical misunderstanding of Baeyer's theory.

Adolf Baeyer proposed his "Strain Theory" (Spannungs Theorie) as an addendum to a paper dealing with the preparation and properties of acetylene compounds (17). The origin of the theory arose from his desire to explain the explosive instability of some of the di- and tri-acetylene compounds, which he suggested was due to some strain in the triple bonds. The extension of this theory to cyclic compounds is added only as a footnote and does not seem directly related to the title of the paper. Baeyer was mainly concerned with the experimental observations relating to the ease or difficulty of ring closure:

> "If a chain of five and six members can easily be closed and one with fewer or more members can be closed with difficulty or not at all, there must be a definite spatial basis for this fact. Any theory of the spatial arrangement of carbon compounds will naturally have to start from ring closure." (18)

Baeyer's theory was based on van't Hoff's concept that the valencies of carbon were directed toward the corners of a tetrahedron:

> "The direction of these attractions can undergo a diversion which causes a strain which increases with the size of the diversion. The meaning of this statement can easily be explained if we start from the Kekulé spherical model and assume that the wires, like elastic springs are movable in all directions. If, now, the explanation that the direction of the attraction always coincides with the direction of the wries is also assumed, a true picture is obtained of the hypothesis outlined in the seventh statement [that is, that the angle between the valencies is 109°28']. If now, as can be shown clearly by the use of a model, an attempt is made to join a greater number of carbon atoms without force, that is, in the direction of the tetrahedral axes, or the wires of the models, the result is either a zig zag line or a ring of five atoms, which is entirely comprehensible, since the angles of a regular pentagon, 108°, differ only slightly from the angle 109°28' which the axes of attraction make with one another. When a larger or smaller ring is formed, the wires must be bent, i.e., there occurs a strain...."

Baeyer then goes on to calculate the angular distortion for rings larger and smaller than the five-membered ring and these are summarized in a figure in the paper:

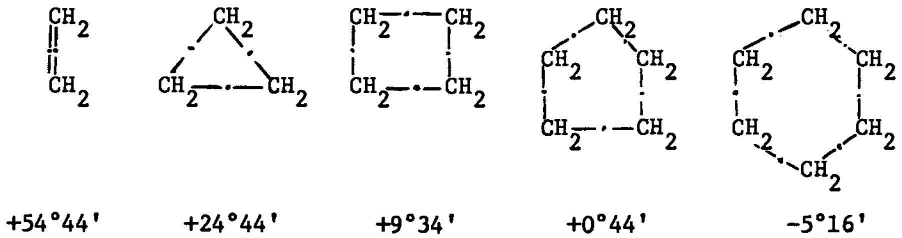


Figure 11. Baeyer's Calculations of Angular Distortion

There are several observations that should be made at this point concerning the preceding quote: 1) the models used were Kekulé models, not van't Hoff models 2) when rings smaller or larger than the 5-membered rings are constructed with the models, the wires must be bent ("like elastic springs"), and 3) the 6-membered ring is strained. As regards the last observation, it is well known to most chemists that when cyclohexane is constructed with the conventional ball-and-stick (or spring) models, the structure obtained is found either in a multiplanar chair or boat form. This was first pointed out by Sachse in 1890 (19). Sachse did not use Kekulé models, but showed how the two forms could be constructed with cardboard tetrahedral models. Sachse's ideas are discussed in more detail in Russell's paper in this volume.

The question that is of concern here is how was it possible for Baeyer to assume the coplanarity of the carbon atoms in the 6-membered ring if he constructed it with Kekulé tetrahedral models? It has generally been assumed that he made this assumption on the basis of the close structural relationship of cyclohexane to benzene:

> "It may be added that as a point of fact six-membered rings have been very frequently found up to now, while five-membered rings occur very rarely and in complicated compounds. However, this objection has no great weight, because the six-membered ring is found almost entirely in the form of a hydrogen-poorer compound, benzene, and it may well be possible that pentamethylene itself, under the same conditions, is a little more easily formed and a little more stable than hexamethylene. I intentionally disregard consideration of thiophene, lactones, etc. in this discussion, because the presence of other elements must be considered."

Victor Meyer later supported this view by suggesting that the stability of the 6-membered ring might be found in its greater symmetry, while also pointing out that the angle of deviation was still quite small (20).

This interpretation of Baeyer has therefore led many chemists to assume that Baeyer must have ignored the facts that would have been revealed to him if he had constructued a model of cyclohexane. In order to demonstrate that this is not so, a closer look must be taken at the models used by Baeyer in the 1880's.

The Kekulé tetrahedral models were first developed in about 1867 and have been discussed in an earlier paper (1). Baeyer had been a student of Kekulé's and not only used these tetrahedral models but apparently modified them in the 1880's. William Henry Perkin, Jr., a student in Baeyer's laboratory in Munich in the 1880's, recounted how Baeyer used them:

> "I remember that on two occasions he invited me into his study and explained to me, with the aid of models that had been specially made, his views on the stability and ease of formation based on the tetrahedral configuration of the carbon atom, and these views gradually gave rise to the 'Spannungs theorie' (21)."

Although it is not clear from this description what the modifications were it is probable that in the Baeyer models the valency wires were joined together by means of a flexible, adjustable joint. Tetrahedral models of this sort which were called: "Kekulé-von Baeyer models" were sold commercially at least as early as 1885 (1), and continued to be sold in Europe and in American until the 1930's. A set of these models that were purchased for use in the Chemistry Department at Eastern Michigan University sometime in the 1920's has been preserved and are used in the following figures to illustrate Baeyer's ideas. When these Kekulé-von Baeyer models are used to construct the "two-membered" and 3-membered ring, it is at once apparent that the wires need not be bent in order to join the atoms (Figure 12):

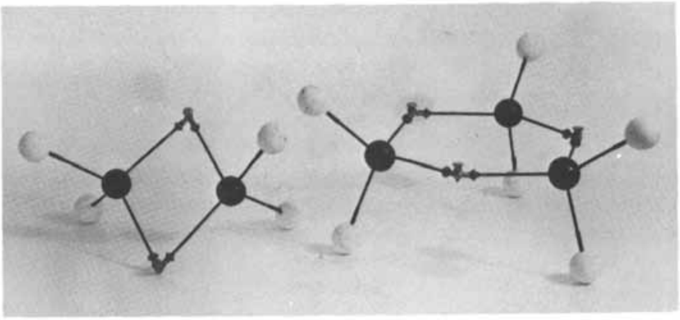


Figure 12. Ethene and cyclopropane constructed with Kekulé–Baeyer models

The "strain" is indicated by the angle between the wires. Which increases as the ring size increases. Note that the tetrahedral angle is maintained in the models and that in the small rings the "direction of the wires" does not coincide with "the direction of the attraction" [see the earlier quotation from Baeyer's 1885 paper]. Although Baeyer's description of the Kekulé models does not correspond exactly with these models, it is difficult to conceive how he could have used a completely different kind of model. It is possible also that for the purposes of illustrating the strain in the carbon-carbon double bond only single wires (or springs) were used.

In 1890, on the occasion of a Kekulé commeration, Baeyer discussed more explicitly the kind of information that would be revealed with these models:

> "A further important property of these models is the angle formed by the wires when certain combinations of the carbon atoms are made. Anyone who has worked with these models will doubtlessly have noticed that these angles almost disappear or even completely disappear if 5 or 6 atoms of carbon are joined together in one ring. Also it should be expressly emphasized that van't Hoff noticed that 6 of his tetrahedra join together in a ring if they are put together with one corner in the direction of the points of attraction. But it seems no one previously tried to explain the significance of the angles made by the axes in other forms, e.g., in ethylene or trimethylene. And yet these are obviously just as important for understanding the constitution of a compound as the spatial conditions are, as I have tried to prove in the so-called 'strain theory' (22)."

Baeyer then goes on to review in more detail how this strain arises. The reason for the lower stability of the double bond compared to the single bond might arise from one of two causes:

> "...either the strength of the attraction as a whole betwen carbon atom and carbon atom is diminished by the omission of two hydrogen atoms; or the fact that the two affinities are no longer operating in the direction they take in methane is to blame. In order to decide this question we can use the behaviour of rings formed of several methylene groups. In these always the same CH_2 groups are joined together; if clear differences can be found in the stability of the bonds here, then this must be attributed to the deflexion of the axes directions, which can be seen from the models. This has now been confirmed as desired, since the ring where there is the greatest deflextion-the trimethylene-is also the easiest to break. I conclude from this that the same reason is valid for ethylene, which can be considered a similar ring to trimethylene."
>
> "This reduction in attraction following a change in direction of the individual affinities can be clarified by a comparison with spring-like wires. However, the normal mechanical process of dispersing the forces in different directions according to the

> parallelogram of forces is not useable here, since an affinity always operates only as a unit, and cannot be dispersed into various ones acting in various directions."
>
> "It must be born in mind that the springs are only an illustration and only serve to explain that a uniform and indivisible force is weakened when it is deflected from the direction it originally held. These are illustrations to demonstrate the conformities with natural laws observed in chemical processes, but they must not be confused with actual processes, any more than one may conclude from the Kekulé model that the chemist who works with it imagines valencies as wires. The force represented visually here by springs will be called tension...."

This passage has been quoted at length to illustrate that Baeyer appreciated the limitations of models in illustrating a theory which attempted to explain the reasons for variation in bonding affinities. The passage also suggests that perhaps two kinds of models were used. The Kekulé models were most likely the ones used to construct the 6-membered ring. The significant aspect of these models is that when the cyclohexane ring is constructed, the "negative" strain in the ring is illustrated by the "bending-in" of the valency wires (Figure 13). Furthermore the tetrahedral direction of the valency wires is maintained even though the six carbon atoms are coplanar!

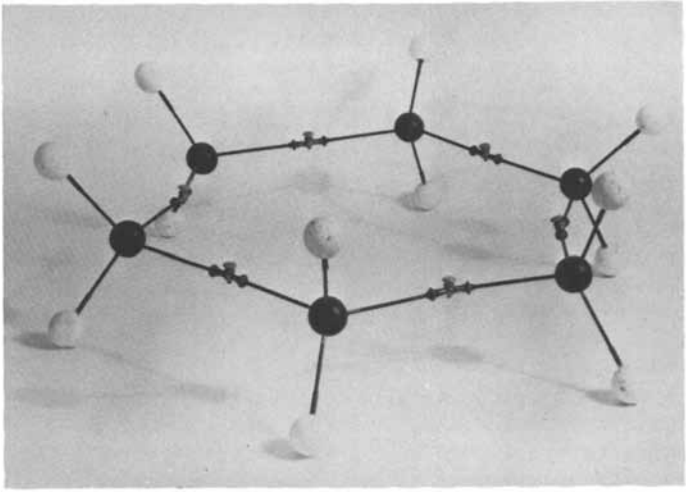


Figure 13. Cyclohexane constructed with Kekulé–von Baeyer models

Did Baeyer himself appreciate this? That this was indeed the structure Baeyer proposed for cyclohexane is revealed in papers published in 1890 and which seems to have escaped the attention of historians. The structure is consistent with his "space-filling" model of benzene suggested in 1888 (23). The figure included in that paper corresponds to the reconstruction with the Kekulé-von Baeyer models shown in Figure 14:

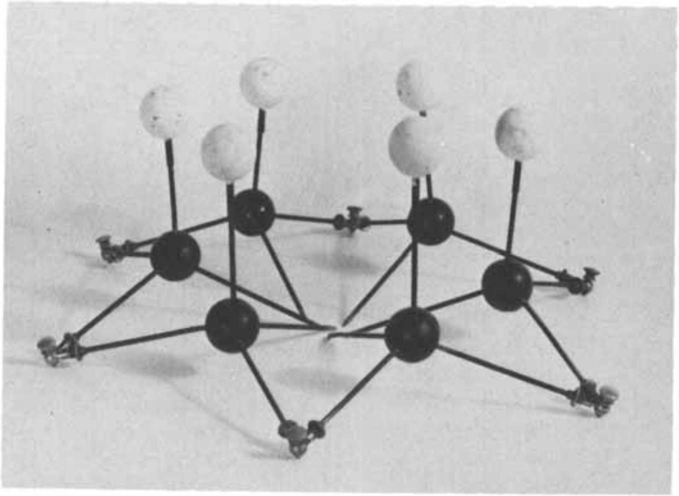


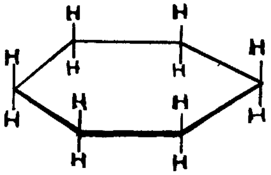
Figure 14. Baeyer's centric formula of benzene

The six hydrogen atoms are all on one side of the ring. The "extra" valencies point toward the center of the ring. Hydrogenation of benzene then saturates these valencies and produces the cyclohexane structure shown in Figure 13. The fact that the hydrogenation of phthalic acid gave the cis- rather than the trans-hexahydrophtholic acid seemed consistent with this structure. The 1888 paper was the first of a series of paper published in the next few years entitled: "About the Constitution of Benzene." The fifth part appearing in 1890 was 74 pages long and and subtitled: "About the Reduction Products of Phthalic Acid" (24). Earlier in the paper in discussing the relationship between benzene and cyclohexane he says:

> "A further pre-condition is that the atoms in the hexamethylene are arranged as the Kekulé model requires, i.e., the atoms are spatially positioned to produce the minimum deflexion of the valency directions. Thus the 6-carbon atoms must lie in one plane and there must be 6 hydrogen atoms in each of two equidistant parallel planes. Further, each of the 12 hydrogen atoms must be in the same position relative to the other 17 atoms. It is relatively easy to test the accuracy

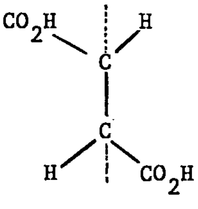
> of this assumption by an experiment. For example, it would be sufficient to show that there is only one hexahydrobenzoic acid. As long as there are so many gaps in our knowledge, we must be content that the above assumption is the most probable and that there is no known fact to contradict it."

A reading of this passage, however, might support a suggestion for a planar structure in which the two sets of hydrogen atoms are situated directly above the carbon atoms; as is found in many of the line drawings used by organic chemists in the latter part of the 19th and first half of the 20th century:

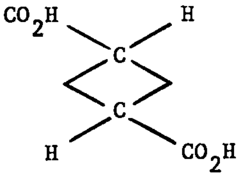


That this was not the structure visualized by Baeyer is indicated by a later discussion in the paper (p. 176-180). In this discussion he asks how it was possible for both the cis and trans forms of hexahydrophthalic acid when treated with acetylchloride to form cyclic amhydrides, when in the analogous cis/trans compoinds: maleic acid and fumaric acid, only the former gave a cyclic anhydride.

> "But a glance at the model [of fumaric acid] will show that the spatial relationships are quite different here; the directions of the valencies binding the carboxyls are exactly opposite and make an angle of 180° with each other; while in fumaroid hexahydrophthalic acid this angle is only a little more than 109°, for the two carbon atoms in question are joined together almost in the original direction of the valencies. This is shown by the figures following, but these cannot give an accurate picture of the angles without reference to the model:



fumaroid
Hexahydrophthalic acid



fumaric acid

> "From what has just been said, interesting conclusions can be drawn regarding the ortho-dicarbonic acids of trimethylene, tetramethylene and pentamethylene. The directions of the valencies associated with the two carboxyls in the fumaroid acids make increasingly smaller angles, as can easily be seen from the model. Therefore, according to the size of this angle, the following series is obtained:
>
> | | |
> |---|---|
> | fumaric acid | 180° |
> | fumaroid orthodicarbonic acid of trimethylene | |
> | fumaroid orthodicarbonic acid of tetramethylene | |
> | fumaroid orthodicarbonic acid of pentamethylene | just over 109° |
> | fumaroid orthodicarbonic acid of hexamethylene | |
>
> Thus one can predict that the fumaric ortho-dicarbonic acid of trimethylene does not give an anhydride, while the fumaroid orthodicarbonic acid of pentamethylene must have the same tendency to anhydride formation as the fumaroid hexahydrophthalic acid. There remains some doubt as to the situation with the orthodicarbonic acid of tetramethylene."

It is therefore clear that when the 6- (or 5-) membered ring is constructed with the Kekulé models, the "dihedral" angle between the carboxyl groups in the trans isomers is only about 109° and not 180° as would be predicted from a structure in which the hydrogen atoms are perpendicular to the carbons in the ring.

Later experimental evidence did not confirm the prediction that trans-cyclopentane-1,2-dicarboxylic acid should also form a cyclic anhydride. By this time, however, other experimental studies that attempted to establish the validity of a multiplanar cyclohexane structure also led to inconclusive results and generally resulted in the chemists' acceptance of the planar structure (25). Thus the concept of the planar, and "strained", cyclohexane ring persisted in the literature of organic chemists for some time in part because no definitive experimental evidence was available concerning the multiplanar structure.

But it might be suggested as a further contributing factor that at least until the early part of the 20th century the models that were available to chemists only allowed the construction of a planar ring. Richard Anschutz in his biography of Kekulé indicates that the original Kekulé models were used at Bonn until about 1909 (26):

> "Since 1909 in the Bonn Chemical Institute we have been using thin springs (wire) instead of the tubes to connect the atom models to each other. This invention of Heinrich Brewer, who at that time was the lecture demonstrator, is especially convenient for small models for private use. Also it enables one to demonstrate the Baeyer

Strain Theory in an illuminating fashion."

The reasons for Baeyer himself considering the cyclohexane ring to be both planar and strained can be better understood from his discussion in the 1890 paper and a more careful consideration of the models he used. The importance of the kinds of models generally available to chemists in the subsequent interpretation and acceptance of Baeyer's Theory has only been suggested and needs further study.

As Professors Prelog and Westheimer have pointed out in their Centennial talks, most organic chemists in the early part of the 20th century did not fully appreciate the information available from the use of models. This was also stated by Haworth (who prepared his own spring models) in 1929 in his book on "The Constitution of the Sugars" (27):

> "Some of the misleading interpretations which have delayed development in the carbohydrate field might have been avoided by more frequent recourse to models as a means of visualizing structural and stereochemical formulae...these considerations [of the conformation of models] open up a large field of inquiry into the conformation of groups as distinct from structure or configuration..."

The shortcomings of the Kekulé models and the non-availability of any suitable commercial models until sometime after the 1920's is also illustrated by the fact that H.G. Derx at Delft felt it necessary to construct special tetrahedral models (Figure 15).

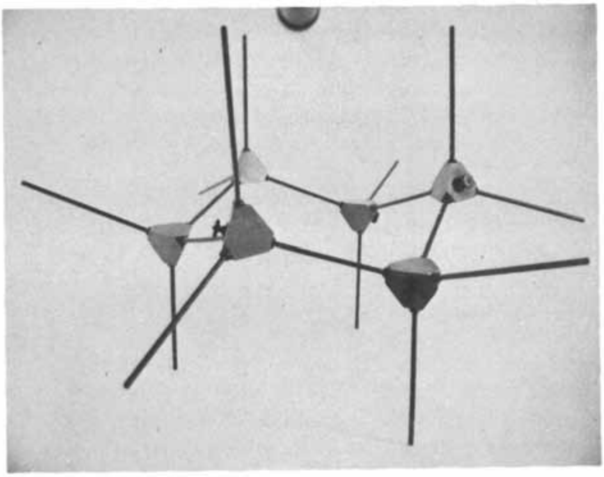


Figure 15. Specially constructed tetrahedral models used by H. G. Derx and by P. H. Hermans in the early 1920's to demonstrate the chair and boat forms of cyclohexane. (Courtesy Technische Hogeschool, Delft)

Photographs of these models were included in an article published in 1922 to illustrate the various chair, boat, and twist forms of the cis- and trans-1,2-cyclohexanediol (28). A short time later P.H. Hermans used the models as the basis for mathematical calculations that demonstrated the greater stability of the chair over the boat form of cyclohexane (29). The various conformations of the 6- and 7-membered ring were also illustrated by Hermans and Maan with Stewart models in 1938 (30). The theoretical and experimental studies of the "Delft" school may well have served as the origin of conformational analysis were it not for the fact that the studies remained almost unknown until recently (25).

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7

Significance and Limitation of Stereochemical Benzene Models

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The Kekulé formula for benzene was a two-dimensional reaction formula and not entirely in agreement with experimental and structural criteria. Baeyer's centric formula emerged as an attempt to explain the properties of benzene with the help of spatial concepts: bond-angle strain and the tetrahedral nature of carbon. This prompted an interest in stereochemical benzene models. Toward the end of the 19th century most of the research on the benzene constitution involved either electrical or stereochemical concepts, or a combination of the two. The use of stereochemical models raised philosophical questions about the ultimate physical reality of molecular structures. Bent of positivist thinking, organic chemists were skeptical about the legitimacy of these models. The resulting discussions provide valuable insight into the philosophical climate of the times.

The rapid rise of experimental organic chemistry in the second half of the 19th century was foremost a consequence of an intense interest in the structure and behavior of aromatic compounds. Aromatic chemistry gained its impetus, mainly in Germany, from the aromatic theory, proposed in 1856 by August Kekulé (1829-1896), Professor at the Belgian State University in Ghent. The theory was designed to explain the behavior of a series of compounds which Kekulé called "aromatic" because many of its members possessed characteristic odors. He suggested that all aromatic compounds contained benzene as a common "nucleus" (1). Furthermore, Kekulé proposed for benzene the hexagon with three conjugated double bonds which is still commonly used as a template and heuristic tool in the study of aromatic reactions (see Plate I).

The aromatic theory emerged partly as a result of Kekulé's researches on unsaturated organic acids. He tried to explain the concept of "unsaturation", assuming the presence of "gaps" in

In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

their structures. Historically, these "gaps" are viewed as the forerunners of double bonds in unsaturated compounds. The "gap theory" also led to the double bonds in benzene (2). On the other hand, the suggestion of a closed hexagonal ring was a consequence of Kekulé's allegiance to the tetravalence of carbon, intuition being a contributing factor. Kekulé himself confessed later that the ring formula had been conceived in a kind of "reverie", in which he imagined long rows of atoms in motion in snake-like gyrations, with one of the snakes grabbing its own tail...(3).

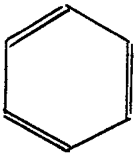
The aromatic theory was generally well received because it filled a gap in a hitherto unexplained area of aromatic chemistry. The Kekulé-hexagon, however, was immediately critisized by many who found it incompatible with the experimental behavior of benzene. The well known lack of "unsaturation" of benzene belied the presence of three conjugated double bonds in the compound, and this consequently became the focus of a long controversy.

The ambiguous nature of the Kekulé-formula provoked a number of alternate benzene symbols which have already been objects of much past and recent discussion (4). For the sake of clarity, they are shown in Plate I. The many attempts to solve the bonding problem of benzene thus took various forms. But, while not all of the proposed symbols were based on a hexagonal ring, the tetravalence of carbon was generally respected. Most of these symbols were originally two-dimensional reaction-formulas, although some people sought to attribute spatial meaning to Ladenburg's prism (5).

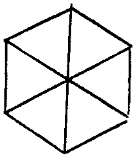
The Controversial Nature of the Benzene Bonds

The existence of so many symbols for this compound of relatively simple chemical composition suggests that the nature of the bonding in benzene was not fully understood. While in practice the Kekulé-formula was used universally and successfully for the prediction and explanation of a growing number of benzene derivatives, in theory the problem of the benzene constitution was far from being solved. From 1866 to 1884, Kekulé and his disciples in Bonn devoted much time and effort to the benzene problem. Kekulé hoped ultimately to prove the constitution of benzene by its synthesis but abandoned this problem after unsuccessful attempts at the condensation of acetaldehyde into a benzene ring (6) (1872) and after some rather unconvincing experiments, involving the cleavage of the benzene nucleus (in the early 1880's).

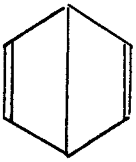
In the 1880's physical methods were applied to benzene, in the hope of determining the nature of its bonding. From the heats of combustion and formation, J.P. Thomsen thought he could verify the presence of only single bonds (7) in benzene, whereas J.W. Brühl's studies on the molecular refraction seemed to support the Kekulé formula with its three double bonds (8). Physical



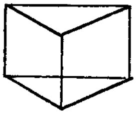
Kekule Hexagon
1866



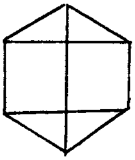
Diagonal Formula
Claus, 1867



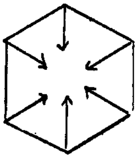
Dewar Formula
1867



Prismatic Formula
Ladenburg, 1869



Projection of
Prismatic Formula
Claus, 1867



Centric Formula
Armstrong, 1887
Baeyer, 1888

Plate I. Conventonal Kekulé Hexagon and alternate benzene formulas

In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

data thus led to contradictory conclusions and contributed to a growing uncertainty about the bonding characteristics of benzene.

In a more speculative way, Kekulé himself had tried to solve the double-bond dilemma by proposing in 1872 a "mechanical hypothesis of valence" (9), (later referred to as the oscillation theory). In this approach, valence was considered as the number of contacts or collisions of atoms with each other in a given unit of time. The oscillation theory represented a trend toward the more "dynamic" explanation of chemical constitution, which became prominent in the 1870's.

On the Origin of Spatial Benzene Configurations

While this dynamic philosophy gained much attention, partly under the influence of a number of debates on the usefulness of the atomic theory in chemistry, another viewpoint of chemical constitution soon came into prominence. In 1874, van't Hoff and Le Bel added a new dimension to chemical compounds by proposing the theory of spatial configuration. For some time, van't Hoff hoped that he could explain not only the existence of various isomers, but that he could also shed some light on chemical bonding. In his book "Ansichten über die organische Chemie" (1881) he tried to connect the valence of an atom with its shape since he considered the "arrangement" of atoms alone insufficient to account for the deeper nature of valence (10). However, Van't Hoff later came to regard these views as mere speculations and of little value to organic chemistry (11).

It is therefore not surprising that the application of spatial concepts to benzene was largely ignored, especially since benzene proved to be optically inactive.

In 1888, however, the stereochemistry of benzene gained in prominence when Adolf von Baeyer proposed a benzene formula with spatial characteristics which he called the CENTRIC FORMULA (12), which I will discuss later (Figure 1).

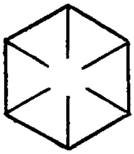


Figure 1. Baeyer's centric formula, 1888

Baeyer was Kekulé's first assistant in Heidelberg and followed him to Ghent in 1858. However, Baeyer stayed there only until 1860 at which time he returned to his native Berlin. Nevertheless he remained very much under the influence of his former teacher for whom he preserved a lifelong admiration. When Kekulé abandoned the benzene problem in 1884, Baeyer took it up, and from 1888 to 1894 he devoted most of his efforts to the elucidation of the benzene constitution.

Baeyer's interest in benzene dates back to his early days in Berlin. Soon after Kekulé had proposed the aromatic theory and his first benzene formula in 1865, Baeyer began to investigate the constitution of certain aromatic acids, especially the phthalic acids, for their relationship with benzene. He reasoned that an experimental verification of the proposed double bonds in Kekule's formula should be feasible if it were possible to demonstrate the connection between phthalic acid and benzene. He then considered reducing the phthalic acids by the same method which Kekulé had used on fumaric acid. For Kekulé, this work had led to the "gap theory," and Baeyer hoped to prove the presence of "gaps" (double bonds) in benzene in a similar way. By decarboxylation Baeyer was able to establish the relationship between benzene and a series of polycarboxylic acids including the phthalic acids (13). But he found the reduction of the phthalic acids rather unrewarding (14) and gave it up when he left Berlin for Strassbourg in 1870. There, he turned to more practical problems and soon became absorbed in his famous research on indigo.

Baeyer had been in Strassbourg for only five years when he was called to Munich as Liebig's successor. Although upon his arrival he found almost no laboratory facilities, he soon was able to build up a model institution which became famous not only in Europe but also in the United States (15).

A.v. Baeyer's Work on the Constitution of Benzene. By 1888, Baeyer was "so fatigued from indigo research and so disgusted with it" (16) that he turned to the study of much simpler compounds, the polyacetylenes, from which emerged his well-known Strain Theory. The Strain Theory proposed that in cyclic compounds any deviation from the "normal" (tetrahedral) angle between the carbon atoms will cause the molecules to be "strained" and therefore more reactive. Since Baeyer considered ethylene a two-membered ring, the Strain Theory allowed him to explain the characteristic chemical behavior of double bonds by a "mechanical principle, bond-angle strain. According to Baeyer the strain in unsaturated compounds was rather high, because the bonds formed an angle of 180^{o} with each other, which represented a large deviation from the tetrahedral angle of 109.5^{o}. Baeyer soon necognized a possible connection between the Strain Theory and the double bonds in benzene. Therefore, in 1888, he once again became interested in benzene research. At that time he wrote:

> The theoretical speculations on the nature of carbon, which I have published in connection with the study of acetylene compounds, demand . . . above all, the elucidation of the benzene constitution.

> This hydrocarbon occupies one of the most important places among the compounds of carbon, on account of its high stability, its ready formation from acetylene, and its close relationship with rings, formed from methylene groups. This has induced me to discontinue the unfinished work on acetylene compounds and to investigate the constitution of benzene instead (17).

Baeyer was convinced that he could not solve the problem of the constitution of benzene without taking into account the spatial relationship between the atoms and the nature of the compound's chemical affinities (die Natur der im Benzol waltenden chemischen Anziehungskräfte) (18).

But above all Baeyer had to decide which of the early benzene symbols (see Plate I) represented most truly the consitution of benzene. In a series of rather ambiguous "proofs" he first elaborated on the relationship between the benzene nucleus of terephthalic acid and hexamethylene (cyclohexane) claiming that hexamethylene was the only product formed in the complete reduction of benzene. Since it is possible to demonstrate the formation of hexamethylene from Kekulé-benzene, but not from Ladenburg's prismatic formula, Baeyer maintained that the prismatic formula could no longer be defended (19). On the basis of his earlier work on the phthalic acids, he then tried to use the carboxyl groups of terephthalic acid as a "marker" to determine the location of the double bonds in its benzene nucleus. He attempted to demonstrate by a logical "proof" that upon reduction the hydrogen atoms always attach themselves to vicinal carbon atoms, and thus rule out the presence of para-bonds. At this point, Baeyer discarded the diagonal formula, although his argument became very shaky later when he realized the possibility of double-bond shifts and consequently he was forced to recant his rejection of the diagonal formula. This brought him into a series of arguments with Claus, who originally had proposed the diagonal formula.

From a constitutional standpoint, this still left as an alternative the Kekulé-formula which seemed to fulfill most of the expected criteria. However, the lack of reactivity of terephthalic acid toward e.g., permanganate and bromine, made the presence of three conjugated double bonds highly questionable. While upon hydrogenation the tetrahydro- and dihydroterephthalic acids exhibited the typical behavior of unsaturated compounds, the terephthalic acid itself appeared to have lost most of its unsaturated character. Baeyer therefore concluded that it "cannot contain double bonds in the conventional sense and therefore the formulas of Kekulé and Dewar . . . must be abandoned . . ." (20) Instead, Baeyer proposed his centric formula, which had neither double bonds nor para bonds.

The Spatial Characteristics of the Centric Formula. For the stereochemistry of benzene, the centric formula represented a step forward, because it was thought to be a three-dimensional formula. In view of Baeyer's great prestige among German chemists, his acceptance of spatial concepts in connection with benzene promoted a new interest in stereochemical benzene models. Before I will elaborate further on this aspect, I would like to discuss very briefly some of the characteristics of the centric formula. In the first of a series of nine publications "On the Constitution of Benzene" which appeared in the *Annalen* between 1888 and 1894, Baeyer displayed his centric formula in graphic form (21) (Figure 2).

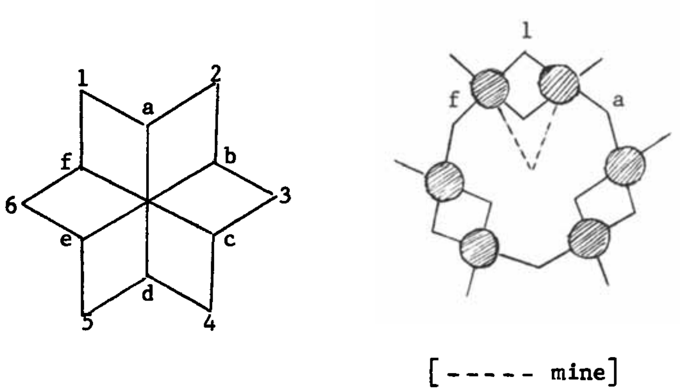


Figure 2. Baeyer's graphic representation of the centric formula and its relationship to Kekulé's first benzene model

Baeyer distinguished between two kinds of bonds in benzene, the central valences and the peripheral bonds (f-1, a-1, etc.). The peripheral bonds were thought to form 60°-angles with each other. The graphic representation of the centric formula bears a relationship with Kekulé's original model (22) (introduced by Kekulé in the second volume of his Textbook in 1866). In the conventional centric formula the central valences were interrupted at the center. Baeyer considered them "passive", or "dormant" and emphasized that they should not be thought of as para-bonds. The nature of the bonding in Baeyer's centric formula suggested a weakening of the tetravalence concept. In fact, Baeyer implied that carbon might be considered trivalent in benzene (23).

Baeyer's Role in the Acceptance of Stereochemistry. Unlike many of his contemporaries Baeyer had a high regard for stereochemistry. He found it regrettable that the spatial concepts of Le Bel and van't Hoff had evoked such distaste among organic chemists, and he hoped that his attitude would encourage the incorporation of stereochemical concepts into organic theory (24). As far as benzene was concerned, Baeyer realized that a stereochemical model might be open to dispute because benzene displayed no optical activity. Attempting to reconcile its optical behavior with the spatial aspects of the centric formula, he suggested that all hydrogen atoms were located on the same side of the molecule in a plane parallel to the carbon ring (Figure 3), which would make the molecule optically inactive. While benzene did not exist in isomeric form, the concept of isomerism worked very well and became fruitful for another class of compounds, the hexahydrophthalic acids (cyclohexane-dicarboxylic acids). Baeyer was able to isolate two isomeric hexahydroterephthalic acids which he named the maleinoid (or cis form) and the fumariod (or trans) form, in analogy with maleic and fumaric acids, respectively (25) (see Figure 4). The extension of stereochemical concepts to cyclohexane derivatives furnished an important method for the identification and isolation of cyclic compounds. Baeyer considered his ideas to be a confirmation of van't Hoff's doctrine of spatial isomerism, and an extension of the stereochemical

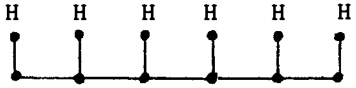


Figure 3. Sideview of Baeyer's centric formula

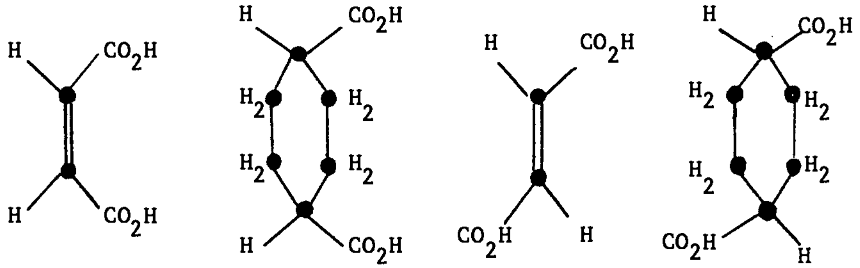


Figure 4. Stereoisomers of hexahydroterephthalic acid

concept to an important branch of organic chemistry. His recognition of stereochemistry helped to promote the new science, and his student, Emil Fischer, proved the validity and utility of stereochemical principles in experimental organic chemistry through his brilliant work on the elucidation of the sugar configurations.

The Limitations of Stereochemical Benzene Models

After 1888, possibly as a consequence of Baeyer's interest in benzene, stereochemical benzene models became prominent and were frequently discussed in the chemical literature. These models were based on various principles of geometrical symmetry, but in general they were derived from the concept of tetrahedral carbon. Among those were the models of Sachse (see Figure 6) and Vaubel (see Figure 7). Since they are generally well known and have been frequently described (26), I have concentrated more on some philosophical aspects involving the general validity of such models. By 1888, the crucial question - the representation of the valence bonds in the benzene molecule - was not yet answered. Toward the end of the century many of the attempts to explain the peculiarities of the benzene bonds involved either electrical or stereochemical viewpoints. Electrical concepts were introduced into aromatic chemistry by Edward Armstrong in England. Spatial explanations, although slow to take hold, eventually, as we have seen, received much encouragement from Baeyer in Germany.

Electrical versus Spatial Views. One year earlier than Baeyer, in 1887, Armstrong had proposed a benzene symbol which was identical with Baeyer's centric formula, although derived from a different route. The centric valences in this formula were meant to express the fact that the "affinity" of the benzene nucleus was somewhat mobile. In aromatic substitution the substituent "tended to alter the distribution of the 'affinity' much as the distribution of the electric charge in a body is altered by bringing it near to another body." (27) In his electrical view of aromatic substitution Armstrong was inspired by Helmholtz who considered valence an electrical phenomenon. In order to explain the bonding in non-polar compounds, Armstrong introduced the concept of "residual affinity" and hoped that it could also serve to explain the constitution and behavior of complex organic compounds, such as benzene. (28)

Ten years later, in Baeyer's Munich laboratory, Thiele expanded Armstrong's concept of "residual-affinity" into the partial-valence hypothesis and applied his theory to the benzene bonds (see Figure 5). Philosophically, Thiele's views on benzene irritated the stereochemists, who considered them a revival of the oscillation theory. As I have mentioned earlier, the oscillation theory represented a trend toward a more dynamic viewpoint of chemical constitution which was apparently incompatible with the static nature of spatial models. The stereochemists, emphasizing "position" rather than "motion," were suspicious of Thiele's partial-valence concept, considering it as an attempt to explain the cause of valence. Stereochemistry had found little satisfaction in the persuit of dynamic and causal principles, and Thiele's concept ran against the grain of the stereochemical philosophy.

Partial Valences in Benzene

Thiele's Benzene Formula (1899)

Figure 5. Partial valences on benzene and Thiele's benzene formula

The Thiele-Erlenmeyer Dispute. Thiele's partial-valence concept thus became a target for criticism which is manifested in a minor controversy between Thiele and Emil Erlenmeyer jun. In 1901, Erlenmeyer attempted to integrate the five basic benzene symbols into a single stereochemical model (Plate II) (29). The model consisted of six regular tetrahedra placed upon an hexagonal ring, and the "critical bonds," main focus of the benzene controversy, were represented by bold lines. Erlenmeyer raised the proposition that the relative positions alone of the tetrahedra involved determined the identity or difference of a compound, not the bonding. He maintained that the bonding in benzene was ambiguous and irrelevant, and that oscillation mechanisms were superfluous.

Erlenmeyer considered Thiele's partial-valence concept incompatible with experimental evidence, especially since it predicted 1,4-addition on conjugated double bonds which very often was not in agreement with the observed facts. On the other hand, Thiele maintained that Erlenmeyer's model was conceptually wrong because it suggested that the edges of the tetrahedra were involved in the bonding in benzene. Since the tetrahedron has six edges, Thiele said, this approach could not be defended. Furthermore, the model suggested the formation of an anhydride of terephthalic acid and other reactions which were in direct conflict with well documented experimental evidence. (30)

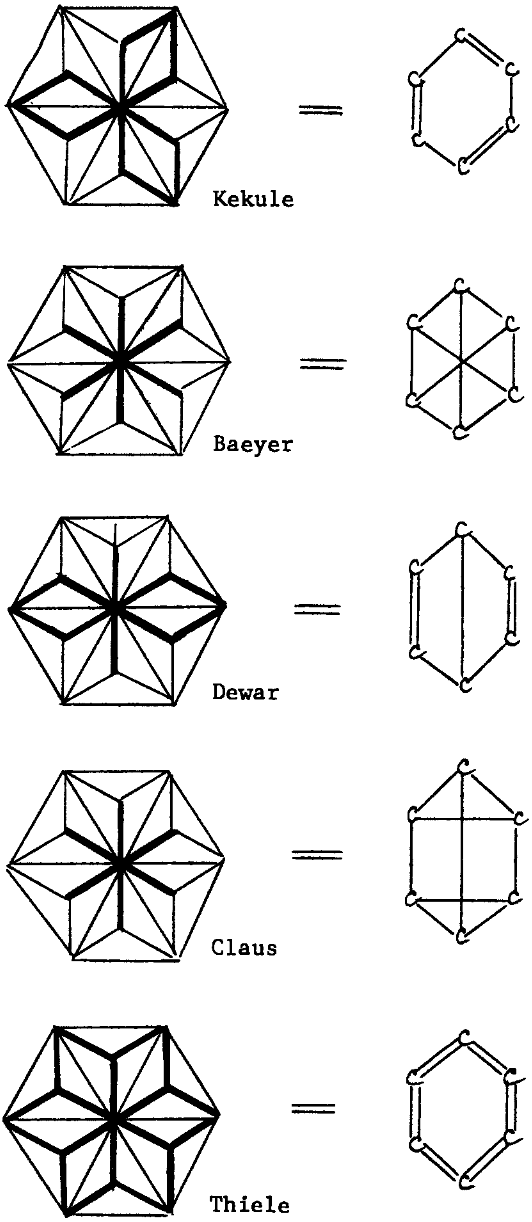


Plate II. Erlenmeyer's stereochemical model

The disagreement also revealed the philosophical differences between the two scientists. Thiele considered Erlenmeyer's views an unacceptable oversimplification of the benzene problem. Erlenmeyer's ideas, although perhaps representing a rather extreme position, were not uncharacteristic for the then current stereochemical viewpoint. By the turn of the century, stereochemistry apparently had subscribed to a largely "mechanistic" philosophy which made it unsatisfactory as a conceptual scheme for the constitution of aromatic compounds.

The Models of Sachse and Vaubel. Antagonistic to the stereochemical philosophy, Thiele also found fault in the models of Sachse and Vaubel. Nevertheless, he considered Sachse's model rather interesting though he generally rejected all speculations which were based on spatial considerations. Sachse's model (1888) (Figure 6) was a three-dimensional extension of the Kekulé-hexagon in which the carbon-valences were represented by tetrahedra.

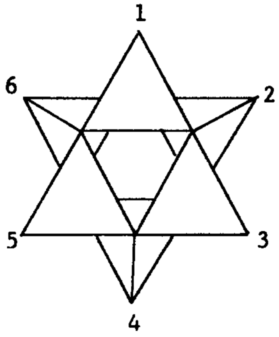


Figure 6. Sachse's model

The single-double bond sequence was indicated by the way the tetrahedra are connected, connection at the vertices representing single bonds and connection at the edges, double bonds. Sachse claimed that his model represented a state of maximum stability in which any oscillation of carbon atoms within the ring system was excluded, thus explaining the chemical stability of benzene (31). His model also represented a purely static viewpoint in direct opposition to the oscillation theory.

Vaubel on the other hand, tried in his model (1894) (see Figure 7) to correlate the geometry of the molecule with its chemical behavior in substitution. As we have seen, Armstrong had considered the relative directive influence of substituents a consequence of the electrical nature of the groups involved. In the stereochemical philosophy, "nature" was replaced by "position".

Vaubel attempted to attribute the directive influence of substituents to the geometry of the model, in which the meta-positions were different from the para-positions insofar as the carbon atoms were closer together in the meta positions. With the help

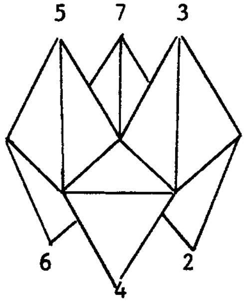


Figure 7. Vaubel's model

of this model, Vaubel thus was able to justify why, e.g., para-dihydroxybenzene (hydro-quinone) was unreactive toward bromine, whereas in the corresponding meta-isomer (resorcinol) bromination occurred readily. Furthermore, in Vaubel's model, the tetrahedra were allowed to flip around their axes, a mechanism which enabled him to explain the formation of phthalic anhydride by the geometry of the molecule. The flexibility attributed to the model of Vaubel indicates a desire to escape the rigidity of purely static viewpoints and to integrate into the stereochemical philosophy certain dynamic principles. Furthermore, he demonstrated a willingness to broaden his concept of the benzene constitution, including electrical viewpoints when, in 1902, he wrote:

> My . . . representation of the benzene nucleus comprises . . . the Kekulé-hypothesis with alternating single and double bonds between carbon atoms. The views of Claus about the centric as well as the diagonal formula are also contained in it. Furthermore, my theory agrees with the views of L. Meyer, v. Baeyer and Armstrong, as well as Thomsen's and Swain's.

Although these are rather sweeping claims, they demonstrate the search for unifying principles. Vaubel apparently was aware of the increasing importance attributed to electrical principles in organic chemistry. Criticizing Sachse's model, he objected to it mainly because it failed to demonstrate appropriately the union of electrical charges (32).

At this point, the stereochemists demonstrated an increasing willingness to abandon a sterile "position-only" philosophy and to incorporate electrical concepts into their spatial views. This was also in agreement with the beginning reconciliation at that time between the old antagonists, the structural and the electrochemical theories.

A Synthesis Between Stereochemical and Electronic Concepts

In the 20th century, one of the most ardent supporters of a synthesis between electrochemical and structural concepts was G.N. Lewis, who in 1916 described the chemical bond in terms of two electrons which act as the connecting links between two atoms (33). Lewis also connected Thiele's partial valences with the presence of unpaired electrons and offered an electronic explanation for the "classical" tetrahedron of the stereochemists. The four corners of the tetra-hedron, Lewis proposed, should be considered as the seat of four electrons, one on each corner, in the single bond, one pair of electrons held in common by the two atoms, in the double bond, two such pairs, and in the triple bond, three pairs

While Lewis himself apparently did not propose an electronic benzene model, his bonding-concept led to the benzene model of Huggins (Figure 8) which bears a resemblance to Baeyer's formula.

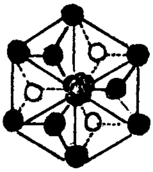


Figure 8. Huggins' benzene model

In Huggins' model, three pairs of electrons were found at the center of the ring and the outer electrons apparently possess a certain degree of single bond character not unlike the peripheral bonds in Baeyer's model. Lewis considered the model of Huggins quite adequate and said that it goes far toward portraying the benzene molecule as we know it (34).

In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

Conclusion

The reluctance of organic chemists to accept stereochemistry in the 19th century must be considered in the light of the prevailing philosophical climate. The "arrangement of atoms in space" implied a belief in the ultimate physical reality of these atoms within the compounds, and hence also the acceptance of the stereochemical models as true representations of reality. In nineteenth-century chemistry, however, such philosophically oriented questions were generally ignored or rejected as mere metaphysical" speculations. This was partly a consequence of the great influence exerted by the positivist philosophy which prejudiced chemists against the search for a "physical reality." The rejection of spatial benzene models by leading chemists, e.g., Thiele, was furthermore justified by the lack of experimental evidence for the existence of a three-dimensional benzene structure.

Baeyer's acceptance of a spatial benzene formula resulted from his desire to justify the strain theory, rather than from his philosophical belief in the actual existence of tetrahedral benzene valences. Baeyer was basically an empiricist at heart, and his theoretical speculations were often less than convincing. In general, we find very little in Baeyer's writing to indicate his concern with problems of physical reality. He used models in the same way as most of his contemporaries. At that time, chemists discussed such concepts as, e.g., steric hindrance with great facility, but they were oblivious of the philosophical implications of such language.

As I have mentioned previously, Baeyer's controversial research on the double bonds in benzene brought him into some minor conflicts with Claus. Baeyer had tried to discredit the diagonal formula as incompatible with the results of his research on terephthalic acid. He accused Claus, furthermore, of ignoring the spatial characteristics of the benzene formula, maintaining that Claus considered the diagonal formula only in two dimensions. Claus rejected this implication, pointing out that one could not speak of symmetry without at least some spatial connotations. Trying, however, to justify the cold and reserved attitude of chemists toward stereochemistry, Claus warned that there was not the slightest experimental proof for the idea that stereochemical formulae were true expressions of the spatial relationship between the atoms in a molecule. "One may ask indeed whether this does not drag something into chemistry which has . . . nothing to do with the chemical behavior of matter, even if one considers stereochemical representations only as pictures." (33)

Such reservations toward stereochemistry were common among a great number of chemists. At Harvard, Arthur Michael, an American who had studied in Germany and France, declared that the hope of determining the arrangement of atoms in molecules was futile, and that he considered the development of chemical theory "hampered exactly by the pursuit of stereochemistry; until the trust in in this hypothesis -- which now has been almost destroyed by experimental evidence -- is eradicated from science (he said), we can hardly expect a noticeable progress." (36)

By the turn of the century, stereochemistry had disappointed many chemists, because contrary to their expectations, it had not brought them closer to an understanding of the physical reality of chemical constitution. In aromatic chemistry, the problem was compounded by the enigmatic nature of the benzene valences, for which, as was later shown, it was difficult to justify from a physical standpoint the assumption of tetrahedral extension. In 1916, Debye and Scherrer applied X-ray analysis to liquid benzene crystals and suggested that, while the symmetry of benzene was hexagonal, all of its atoms were located in the same plane.

In the "classical" sense, stereochemical benzene models belong now to history. But the philosophical questions they raised will be of lasting interest.

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8

The Conceptual Premises of Conformational Analysis in the Work of C. A. Bischoff

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The history of conformational analysis usually begins with the well-known work of Barton (1), after which chemists generally began to understand the importance of studying the conformational composition of organic compounds for the determination of chemical reactivity (2). However, the study of the relative energetic stability of different conformations of the same compound, the properties of the latter as a function of its conformational composition, and the nature of the separate primarily preferred conformations began earlier than the name conformational analysis was adopted (3) and gained its place as a subject of independent interest in the field of stereochemistry. These studies even predate the physical chemical and spectroscopic studies in the 1920's and 1930's that were concerned with the idea of a rotational barrier about the C-C single bond.

If we try to find the starting point for the study of rotational isomers, however, we must return to the last third of the nineteenth century, to the numerous examinations of the so-called "second hypothesis of van't Hoff", by which Auwers and Victor Meyer (4) supposed a proposition of free rotation around a single bond and the possibility of isomerism only in those cases in which by rotation around a given bond one form could not be converted into another. The impulse for the testing of this idea of van't Hoff was given by the fundamental work of Wislicenus (5) who postulated that substituents on two atoms of carbon joined by a single bond could prevent free rotation, with the formation of a preferred configuration, or, speaking in modern terms, conformation. However, Wislicenus erroneously assumed that limitation of rotation around a single bond depended on the force of attraction ("not only gravitational, but also of a chemical character") between the substituents on a given pair of carbon atoms.

In this connection we should recall the work of the Riga professor Carl Adam Bischoff. He was the first (in 1890) to raise the question of the existance of rotational ("dynamic")

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Carl Adam Bischoff

isomers depending on the force of repulsion, first assuming an alternating configuration for locating the substituents, and using a method of denoting rotational isomers which, in more or less modified form, is still used today. We can also show a direct connection between the ideas of Bischoff and Sachse.

From the brief papers that are published in memory of Bischoff (6, 7) we know that he was born April 8, 1855 in Wurzburg. In 1873 he entered the medical faculty of the local university, but after two years, influenced by the lectures of Wislicenus, he turned to chemistry. Bischoff worked for some time with Fresenius and Bunsen, and then returned to Wurzburg. He obtained the degree of Doctor of Philosophy there in 1879 with work on homologs of acetopropionic acid. From 1881 Bischoff was a privat docent and assistant to Wislicenus. In 1885 Bischoff followed Wislicenus to Leipzig, at first as privat docent, and after 1886 as extraordinary professor. In 1887, on the advice of Wislicenus, Bischoff accepted the chair of chemistry in the Riga Polytechnic Institute, vacant after the transfer of Ostwald to Leipzig. In the Institute Bischoff at first taught inorganic and organic chemistry, and after 1898 only organic chemistry. The excellence of his teaching, especially in the practical work, and the training of many students who later made a name in science gave Bischoff such authority that, in spite of the introduction of obligatory lectures in Russian in 1896, Bischoff was allowed as an exception by the Ministry of Education to give his course in the German language. Among the numerous students and coworkers of Bischoff we should note Paul Walden, on whose training in stereochemistry Bischoff exerted a great influence (8). Heart disease forced Bischoff to retire in the spring of 1908 and go to Germany. An unexpected attack of appendicitis, in spite of an operation, ended his life there on October 18 of the same year.

In the course of his scientific activity, Bischoff followed two paths: organic synthesis and stereochemistry. His synthetic work was connected chiefly with testing theoretical ideas relating to the effect of the steric structure of organic compounds on their reactivity, especially on their ability to cyclize. The synthesis of mono-, di-, and trisubstituted succinic and glutaric acids which he carried out before his call to Riga gave him experimental material for his hypothesis of the nature and role of "dynamic isomers." It is certain that the work of Wislicenus already mentioned (5) served for a while as his theoretical basis. In general methodological plan, as Bischoff himself (9) and also Walden (10) showed, he was influenced by the work of Beketov, especially as expressed in the lecture "The Dynamic Side of Chemical Phenomena" (11). A direct impulse for the first paper of Bischoff was the appearance of the work of Meyer and co-workers on the testing of the "second hypothesis of van't Hoff" (4, 12). In particular, Meyer and Riecke proposed an electrostatic model of the chemical bond (dipole-dipole interaction) in the case of a single bond assuming (and in the case of a double bond not assuming) rotation around the bond formed by two atoms of carbon (12).

The question propounded by Bischoff was different. He considered that the formation of anhydrides of substituted succinic acids was the result of "intramolecular motions" of the hydrogen atoms and hydroxyl groups which when they encountered each other, reacted with the evolution of water. Bischoff raised the question: what will happen if under these conditions the alkyl groups also encounter each other? His answer was that the accumulation of alkyl groups should result in a restriction of the vibrations of the atom-systems which were joined by the single bond. The result would be a partial limiting of the rotation about the single bond. This would lead to the formation of geometrically isomeric configurations, that is, isolatable conformational isomers. In contrast to Wislicenus and other authors who assumed that a restricted rotation depended upon attractive forces between the substituents, Bischoff postulated that the rotation was restricted by "the filling of the space by the radicals and in the decreased distance of the carbon atoms from each other which depends on this" (13).

According to Bischoff's "dynamic" hypothesis, that configuration (conformation) is preferred in which the separate parts of the molecule hinder their relative vibrations to the least degree. From this point of view, then, ethane can be designated by the second symbol in Figure 1 rather than the first (14).

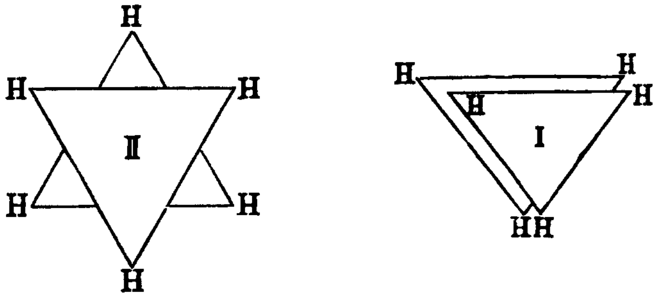

Figure 1

When Bischoff introduced these symbols he noted that "such a designation, naturally, represents an helpful idea which to some extent replaces a model" (15). In order to decide on which configuration of the substituted succinic acids would be the favored one, Bischoff made three assumptions, which he assumed rested on experimental data:

1. The carboxyl group is repelled by a carboxyl group - an idea already proposed by Wislicenus.
2. The methyl group is repelled by the methyl group. This

contrasts with A. Baeyer, who felt that the methyl groups should be attracted to each other.

3. The carboxyl group is repelled more strongly by the methyl group than by a carboxyl group. According to Wislicenus, the carboxyl group is attracted by a methyl group. Thus, for example, in the formation of succinic acid from the hydrolysis of succinic anhydride (Figure 2), the succinic acid ends up in (in modern terminology) a conformation in which the carboxyl groups are in an anti conformation, although the initial reaction would produce a conformation in which the carboxyl groups were in a gauche conformation.

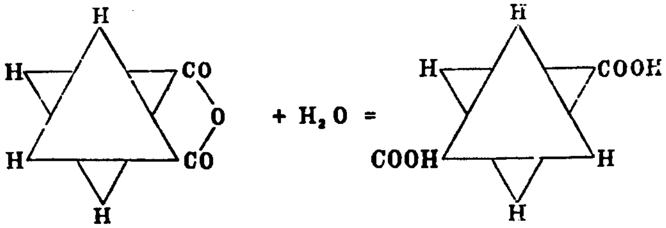

Figure 2

The introduction of methyl substituents might change the preferred conformation. Although the introduction of one methyl substitution (Figure 3) was not thought to affect the conformation, the introduction of additional groups increased the number of methyl-carboxyl repulsions to such an extent, that the preferred conformation would be that in which the carboxyl groups were closer together (Figure 4–6).

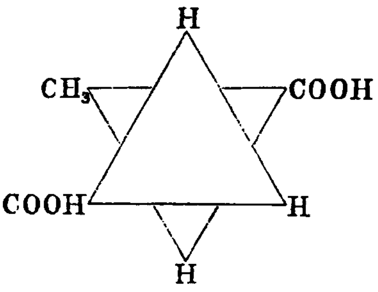

Figure 3

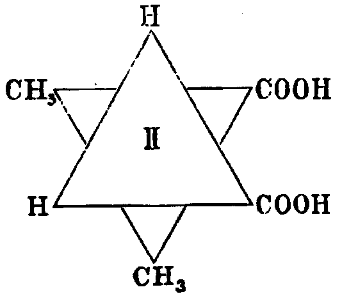

Figure 4

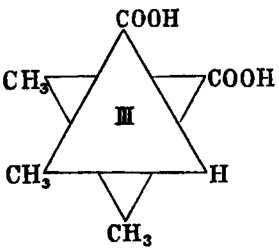

Figure 5

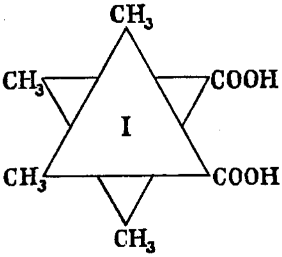

Figure 6

To judge the reactivity of these compounds, especially their ability to form the cyclic anhydrides, Bischoff considered it necessary to consider not only the preferred configurations as expressed in these formulas, but also to consider the fact that they introduction of the alkyl substituents should affect the distances between the "triangles" and also change their form. In symmetrically substituted compounds, such as tetramethylsuccinic acid, and in other multisubstituted ethane derivatives, Bischoff felt free rotation of the system around the common axis is limited and can only occur within narrow limits, which he indicated with arrows (Figure 7).

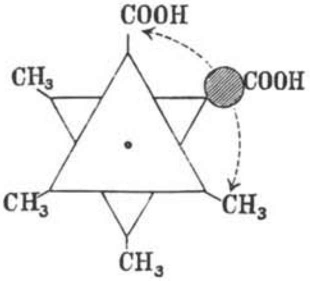

Figure 7.

Of course, heat impulses can sometimes raise the energy of the system so that the groups bound to the carbon atoms turn about and one isomer passes into the other. To these isomers Bischoff, following Beketov, assigned the name "dynamic isomers."

Bischoff explained his ideas in systematic form not only in separate papers, but also in R. Meyer's Jahrbuch der Chemie for which Bischoff contributed a section on organic chemistry for a number of years (16). The hypothesis of the existence of "dynamic isomers" in a series of substituted succinic acids was not confirmed experimentally, however, and the facts which initially seemed to support it were found to be incorrect. This Bischoff himself recognized (17) and even declined the corroboration of of his hypothesis that was suggested by the studies of Zelinsky and Bezredka (18).

Several months after the publication of Bischoff's first article, there appeared in the same journal the well-known work of Sachse (19) which postulated the existence of two "normal configurations" of cyclohexane. As an explanation of the change from one to another of these configurations Sachse later gave an even more fully developed hypothesis of delayed rotation around a single bond. In particular, the repulsion of atoms joined through two atoms of carbon led, according to Sachse, both to a divergence from the true tetrahedral form and to a "rotation of one of the two tetrahedra round the C-C bond" and then the system was not in equilibrium (20). Sachse even gave orienting calculations to establish the angle of rotation. For example, for trimethyl succinic acid he found that the angles of rotation (from the position in which the carboxyl groups were found one over the other) were 201° and 159°, but nevertheless he assumed that for such compounds only one "normal" configuration was possible.

Somewhat earlier Sachse had used the expression "dynamic isomers" for designating the "normal configurations" of cyclohexane which could easily change into each other. He asserted that since not one of the dynamic isomers expected according to the "dynamic theory" of Bischoff had been obtained, Bischoff had abandoned his theory and therefore the term remained "free" (21).

Bischoff agreed fully with the use of the term "dynamic isomers" by Sachse, but he noted that this did not mean that he denied the validity of the theory of dynamic isomers. "From the very beginning," wrote Bischoff in his textbook on stereochemistry, "I have tried to establish an understanding of 'dynamic isomers' in the sense also understood by Sachse." The fact that the report of the existence of an isomer of trimethylsuccinic acid had not been confirmed (it seemed that this isomer was dimethyl glutaric acid) it did not at all follow that isomers in the "dynamic sense" could not be found in other bodies. "As I previously firmly believed, the present state of our knowledge obviously has not exhausted all possible varieties of isomers, and to find them a method must be used which has in many cases already been shown useful, namely: the use of definite hypotheses as guides" (8). Moreover, in the same textbook Bischoff gave numerous examples of the use of these hypotheses in organic compounds of different classes. In particular, for the carbon skeleton of cyclohexane "the idea of isomers in the dynamic sense leads to the following symbols in which the original angles between the valencies of carbon remain the same as in the regular tetrahedron (Figure 8). One form can change into the other without change of bonds (ohne Bindungswechsel). The amount of resistance to this change depends on the nature of the combined atoms" (8).

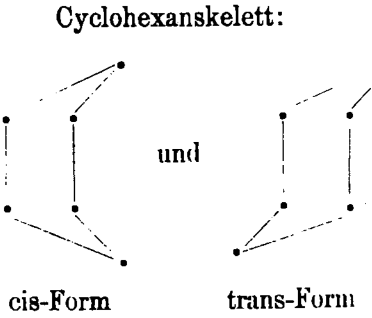

Figure 8

The contemporaries of Bischoff appraised differently his hypothesis of the existence of dynamic isomers (conformers in the modern sense of the word). For example, Werner stated that "it is not expedient to go so far in explaining the reason for the steric action of groups" to account for the difficulty posed by the direction of some reactions, and noted that the basic characteristic of the Bischoff hypothesis as the postulation of a repulsion of atoms during their intramolecular motion (22). Walden, as already mentioned a close co-worker with Bischoff in the preparation of the textbook on stereochemistry, in his note in memory of Bischoff (7) wrote that the idea of "dynamic isomers" and the "dynamic theory" was too mechanistic (zu mechanistisch). In his "History of Organic Chemistry" Walden cited several propositions by Bischoff from his first work on dynamic isomers without giving him any appreciation or allotting him a definite place in the history of stereochemistry (23). Other historians of organic chemistry and authors of textbooks on stereochemistry also limit themselves to short mentions of the work of Bischoff or pass over his work in silence, although Bischoff was the first among those who offered important ideas used by contemporary scholars concerned with rotational isomers and conformational analysis, including the presently used method of describing conformations known under the name of the Newman projections. Such neglect of the work of Bischoff in the past is understandable; a just estimate of it could not be given from the theories of stereochemistry at the end of the nineteenth century. It can take place only in the second half of the twentieth century.

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9

Has van't Hoff been Well Read and Understood by the Profession?

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At the occasion of the world wide held van't Hoff - Le Bel centennial commemoration in 1974, the present highly aged author has been bestowed by with several marks of honor for having been one of the group of young Dutch workers, now called the "Delft School", who first irrevocably proved the non-planarity of the carbon rings beyond five carbons (H.G. Derx) and laid the fundamentals of Conformational Analysis by definitely proving the existence of a "barrier to rotation" (P.H.H.) as well as providing also the first quantitative measurement of a barrier to rotation on an exact thermodynamic basis (1, 2, 3).

In this way, the early Dutch work in question, which remained generally ignored for half a century, even in all modern textbooks and historical reviews, was repeatedly brought to public attention. Although this (whatsoever belated) acknowledgement should be appreciated as such, the present author does not agree with location of the very origin of Conformational Analysis in his own early work.

In his personal view it should be ascribed to van't Hoff himself, a fact which seems to have been quite generally overlooked by the profession as well as by its historians. It is an undisputed fact, that the origin of stereochemistry should be traced back to the Dutch Chemist van't Hoff who shares this merit with the Frenchman Le Bel.

Much less well known - at least less well remembered today - is, that the pioneering papers by van't Hoff at first have met with a fierce criticism, composed in quite discourteous, if not improper wordings, authored by a recognized organic-chemical "authority" of the time. It was the German chemist Kolbe, who published his rejecting and almost insulting criticism (in J. Prakt. Chem.). He even used in it the word "charlatanerie" (mountebankingness) to characterize his judgement! (It has meanwhile been revealed that, several years later, in an advise related to van't Hoff's admission as a member of the Royal Academy of Science in Amsterdam, the well-known Dutch professor of Chemistry Franchimont wrote about van't Hoff: "His work is very

In van't Hoff-Le Bel Centennial; Ramsay, O.;
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superficial and he is too soon contented with it, ---thr´oroughness, which one likes to see as a mark of lasting value, is lacking." His conclusion: van't Hoff was not eligible as a member of the Academy.)

One of the most eye-catching aspects of the van't Hoff - Le Bel concept of carbon chemistry was rotation about the single C-C bond. This concept was indispendable in their doctrine in order to avoid prediction of more isomers in ethane derivatives, than those actually observed.

From that very moment onwards (and for some mysterious reason) the concept of free rotation spread itself like an ink blot through the whole of chemistry, even becoming a current term normally used by every chemist. This has been a fatal error which one should merely see as an invention ad hoc by unattentive colleagues, who could permit themselves superficial thinking.

In this connection one should not forget that - at this time- the majority of so-called organic chemists were but poorly trained in physics and preferred to operate with easily understood qualitative ideas; quantitative thinking often but induced their aversion.

It has been generally overlooked, at the time, (and I believe it is even still so at present), that van't Hoff himself has never intended to propagate free rotation. He was a far too clever and physically trained mind to do so! In fact, one has only read him superficially. I dare to claim this in spite of the fact that in the second edition of his famous book: "Die Lagerung der Atome im Raume" (The position of atoms in space) one finds even a chapter entitled "Free rotation" (4). In my personal view it may, however, be taken as dead sure that - here - he has exclusively intended to refer to a geometrical aspect of the matter, and not to a really physical one.

I suppose that - well knowing his customers of the time - he held a pedagogical motive for acting so. He asked them to make a spiritual somersault, and probably did not wish to take a risk of rendering it too difficult for them all at once. If my supposition is correct, history has well proven him to have done the right thing.

Primarily, no misunderstandings nor problems should arise with regard to the number of isomers; the issue of isomers should not fail. Free rotation was a good guide to isomers.

Irrevocable proof of my claim that van't Hoff himself was quite aware of the true situation correctly, is found in his book: "Dix annees dans l'histoire d'une theorie" (published in 1887) (5). Here, one finds a subchapter on hexa-substituted ethanes, along with a discussion of the isomers of malic acid, clearly demonstrating that proof. I shall quote some sentences from that writing in order to enable everyone to judge for himself (free translation from French): "It is very probable that among the numerous isomers rendered possible by rotation about the C-C bond, some are particularly favored and thus will predominantly occur" - and further: "That it is not excluded that once, one will be in the position to establish which they are."

van't Hoff then speculated which ones are probably thus favored in the case of malic acid. He let himself thereby be guided by the thought that pronouncedly "negative groups" (as e.g., hydroxyl and carboxyl) will avoid coming too close to each other.

The preferred conformations which he then proposes are exactly the ones which we take for granted today. In my view it is here and nowhere else, where we find the very origin of "Conformational Analysis": with van't Hoff himself in 1887.

I want to ask the question if any one has been taught these facts before. It would seem that they have been entirely overlooked. In no modern textbook have I ever found a single word about this matter. Contrarily, all modern authors, when introducing conformational analysis, start off with the statement that rotation is not "free", thus emphasizing the suggestion that the concept of free rotation would represent a generally rusted-in error, not corrected until "modern times".

This is, however, as I hope to have pointed out, all but true. During about half a century the ship of Chemistry has towed this error along and has been held back in her progress by missing an important guiding principle, until the "Delft School" definitely cut the towing cable, without being ever acknowledged or referred to for that essential action until another half a century later. Meanwhile numerous false priorities in the field of conformational analysis have been assigned to much later authors, and stubbornly transpired into the literature. A conspicuous example is the predominant stability of the chair form of cyclohexane, which was experimentally as well as theoretically well established by the "Delft School", as early as 1924, but "officially" did not emerge for several decades later (1).

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10

The First Resolution of a Coordination Compound

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Coordination compounds could not be accounted for in terms of Kekulé's valence theory, which, although so flexible and fruitful in the organic realm, proved to be a virtual straitjacket when applied to inorganic chemistry (1). Although Frankland, Couper, and other pioneers in valence theory readily admitted the possibility of variable valence, Kekule, throughout his lifetime, dogmatically insisted, in opposition to experimental facts, that "atomicity [valence] is . . . a fundamental property of the atom which is just as constant and unchangeable as the atomic weight itself" (2). In order to maintain this simple, admittedly attractive principle, Kekulé designated as molecular compounds a large number of compounds formed by the union of molecules, the valences of whose atoms are already saturated. Foremost among such compounds inexplicable by the doctrine of constant valence were the ammonium salts, double salts, metal salt hydrates, and metal-ammines.

While Kekulé dealt with metal-ammines by banishing them to the limbo of "molecular compounds," other chemists enunciated elaborate theories to explain their constitution and properties (3-5). In 1893 Alfred Werner, the founder of coordination chemistry (6), proposed his revolutionary coordination theory, which marked an abrupt break with the classical theories of valence and structure (7). He postulated two types of valence--primary or ionizable (Hauptvalenz) and secondary or nonionizable (Nebenvalenz). According to Werner, every metal in a particular oxidation state (primary valence) has a definite coordination number, i.e., a fixed number of secondary valences that must be satisfied. Whereas primary valences can be satisfied only by anions, secondary valences can be satisfied not only by anions but also by neutral molecules such as ammonia, water, or organic bases. These secondary valences are directed in space around the central metal atom (octahedron for coordination number 6; planar square or tetrahedron for coordination number 4), and the combined aggregrate forms a "complex", existing as a

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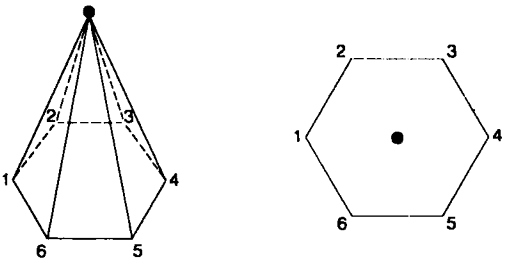
discrete unit both in the solid state and in solution (8, 9).

The technique of "isomer counting" that Werner used to prove the configuration of cobalt-ammines (coordination number 6) did not originate with him, but this technique of comparing the number and type of isomers actually prepared with the number and type theoretically predicted for various configurations probably reached the zenith of its development with his work. By this method, Werner was able not only to discredit the rival Blomstrand-Jørgensen chain theory but also to prove that tripositive cobalt possessed an octahedral configuration rather than another possible symmetrical arrangement such as hexagonal pyramidal, hexagonal planar, or trigonal prismatic. The results of the method are summarized in Figure 1 and Table I.

As a comparison of Columns IV and V of Table I shows, in most cases the number and type of isomers prepared corresponded to the expectations for the octahedral arrangement, but there were a few exceptions and missing compounds, and Werner required more than twenty years to accumulate a definitive proof for his ideas. In 1907 he finally isolated the unstable, highly crucial violeo tetraammines, cis-$[Co(NH_3)_4Cl_2]X$ (Compound Type MA_4B_2), that were a necessary consequence of his theory but not of Jørgensen's (10). His Danish opponent immediately conceded defeat. Although this discovery convinced Jørgensen that his own views could not be correct, Werner's success in preparing two—and only two—isomers for compounds of types MA_4B_2 and MA_3B_3 was insufficient to prove conclusively the octahedral configuration. Despite such "negative" evidence, one could still argue logically that failure to isolate a third isomer did not prove its nonexistence. A more "positive" proof was necessary, and this proof required the resolution of asymmetric coordination compounds into their optical antipodes.

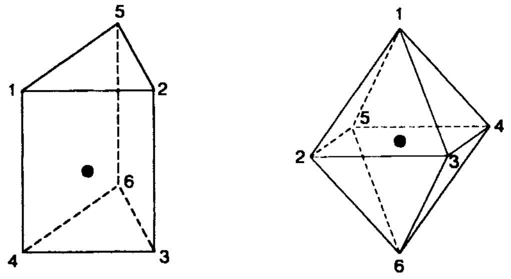
In 1890 Le Bel and van't Hoff's tetrahedral concept of 1874 had been successfully transferred from the carbon atom to the nitrogen atom by Werner and his mentor, Arthur Hantzsch, who used the concept to explain a number of hitherto unexplained cases of geometric isomerism among trivalent nitrogen derivatives, especially the oximes and related organic compounds (11). In his first paper on the coordination theory (7), Werner applied the tetrahedral model to what were then known as "quinquevalent" nitrogen compounds—the ammonium salts (12). Once it was realized that atoms other than carbon could possess a tetrahedral configuration, stereochemistries for various elements were proposed and experimentally proven.

Although compounds containing asymmetric atoms other than carbon, e.g., nitrogen, phosphorus, sulfur, selenium, tin, and silicon, had been resolved before Werner's resolution, all these cases had involved atoms of tetrahedral configuration. Werner's work, however, involved a compound of the proposed but as yet unproven octahedral configuration. As a result of this work, Sir Gilbert T. Morgan was able to state in his obituary of Werner



I
Hexagonal Pyramidal

II
Hexagonal Planar



III
Trigonal Prismatic

IV
Octahedral

Figure 1. Configurational possibilities for coordination number six

Table I. Proof of Configuration for Coordination Number Six by "Isomer Counting"

	Theoretically Predicted Isomers				Experimentally Found Isomers	
Compound Type	I Hexagonal Pyramidal	II Hexagonal Planar (A Special Case of I)	III Trigonal Prismatic	IV Octahedral	V	Result VI
MA_6	One Form Only	One Form Only	One Form Only	One Form Only	One Form Only	None
MA_5B	One Form Only	One Form Only	One Form Only	One Form Only	One Form Only	None
$M(\overline{AA})B_4$*	One Form Only	One Form Only	Two Geometric	One Form Only	One Form Only	Provisionally Eliminates Trigonal Prismatic(III)
MA_4B_2	Three Geometric (1,2;1,3;1,4)	Three Geometric (1,2;1,3;1,4)	Three Geometric (1,2;1,3;1,4)	Two Geometric (1,2 cis; 1,6 trans)	Two or Less Geometric	Provisionally Proves Octahedral (IV);Discovered 1907
MA_3B_3	Three Geometric (1,2,3;1,2,4; 1,3,5)	Three Geometric (1,2,3;1,2,4; 1,3,5)	Three Geometric (1,2,3;1,2,5; 1,2,6)	Two Geometric (1,2,3 facial; 1,2,6 peripheral)	Two or Less Geometric	Provisionally Proves Octahedral (IV)
$M(\overline{AA})B_2$* or $M(\overline{AA})BC$*	Two Geometric	Two Geometric	Four Geometric, one of which is asymmetric	Two Geometric (1,2 cis; 1,6 trans), the first of which is asymmetric	Two Geometric (1,2,cis;1,6 trans), the first of which was resolved	Unequivocally Proves Octahedral (IV);Discovered 1911
$M(\overline{AA})_3$*	One Form Only	One Form Only	Two Geometric	One Asymmetric Pair	One Pair Optical Resolved	Unequivocally Proves Octahedral (IV):Discovered 1912

*$\overline{AA}$ represents a symmetrical bidentate (chelate) ligand. Such ligands coordinate at two adjacent positions. They can span cis positions but not trans positions.

that "the spatial configuration of the coordination complex with six associating units is now as firmly established as that of the asymmetric tetrahedral carbon atom" (13).

Werner's Earlier Work

Werner was trained as an organic chemist and was an authority on organic stereochemistry. As early as 1896 one of his *Doktoranden* was investigating the optical activity of organic compounds (14). Werner's first published work in the field of optical activity, the resolution of *trans*-hexhydrophthalic acid, appeared in 1899 (15).

We do not know exactly when Werner first realized that one of the geometric consequences of his octahedral model was molecular asymmetry for certain types of complexes containing chelate ligands or when he first recognized that a resolution of such compounds would provide an elegant and definitive proof of his stereochemical view that cobalt(III) possesses an octahedral configuration. Contrary to common belief, no mention of this topic appears in his first paper on the coordination theory (7).

According to Victor L. King (Figure 2), Werner's American *Doktorand* who successfully solved the problem, Werner and a series of his students had been attempting to resolve coordination compounds for "over a period of some nine years" (16), which would date Werner's first experiments from about 1902. However, the first direct, documented evidence that Werner was actively engaged in experimental attempts to resolve coordination compounds is found in a letter of February 20, 1897 to his friend, former classmate, and collaborator Arturo Miolati (17): "At present we are searching for asymmetrically constructed cobalt molecules. Will it be successful?" Thus King's estimate of the time expended by Werner on the problem was a conservative one.

In 1899, in a paper dealing with oxalatobis(ethylenediamine)-cobalt(III) salts, Werner considered the possibility of optical isomerism among coordination compounds for the first time in print:

> On the basis of the octahedral formula, spatial consideration of the radical
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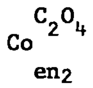
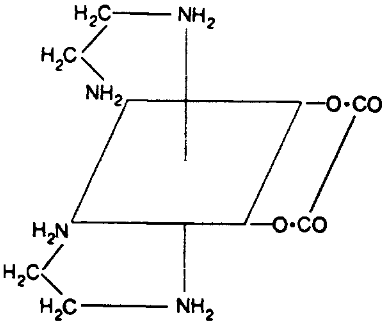
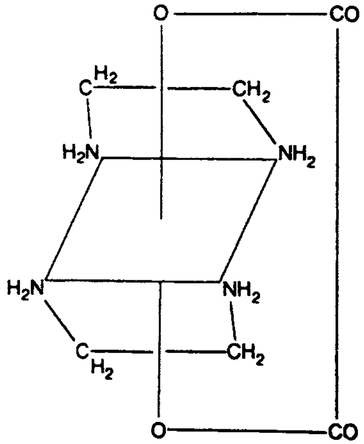
> 
>
> $$\mathrm{Co}\begin{matrix}C_2O_4\\ en_2\end{matrix}$$
>
> leads to interesting consequences in regard to the appearance of a new possibility for isomerism. By analogy we must conclude that the most probable bonding of the residue
>
> $$\begin{matrix}O{:}C{\cdot}O{-}\\ O{:}C{\cdot}O{-}\end{matrix}$$

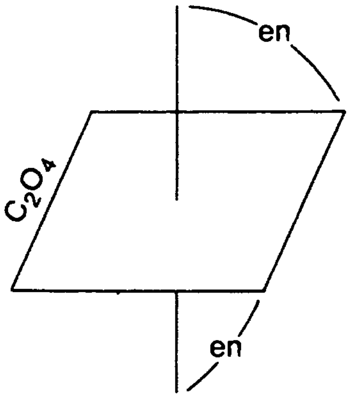
will be the one in the edge position of the octahedron and not the one in the diagonal position, that is:

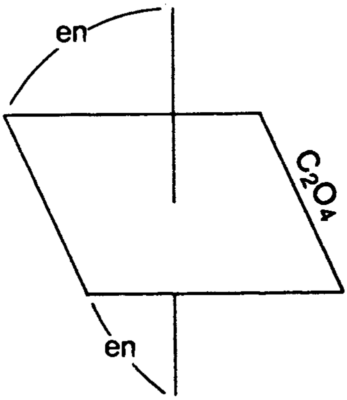


and not

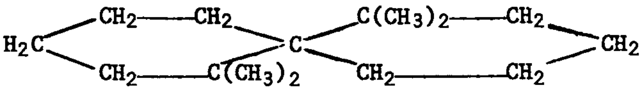


The model resulting from this assumption, however, is stereochemically speaking an asymmetric one; i.e., it can be construed in two spatial arrangements which behave as image and mirror image and which cannot be made to coincide,



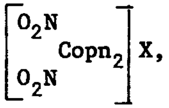


The case of isomerism developed here is not comparable to the usual asymmetry in organic molecules which, as is well known, is stipulated by so-called optical isomerism, inasmuch as the groupings (2 ethylenediamines) which are here arranged right or left are identical. The above isomerism would rather be comparable to that of organic double ring systems; e.g., of the following type:



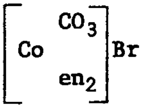
> which can likewise be construed in two nonsuperimposable models acting as image and mirror image even though no asymmetric carbon atom is present. Among carbon compounds too, this type of asymmetric isomerism has until now not been observed. Thus, for the oxalatodiethylenediaminecobalt salts and similar compounds, we may predict a new type of isomerism which belongs to the class of asymmetry isomerism, of which until now the usual carbon asymmetry and the molecular asymmetry of the inositols are known (18).

Eight years later Werner had not attained his goal, for on November 15, 1907 he wrote to the Russian chemist Lev Aleksandrovich Chugaev (19):

> I see from your beautiful paper in Berichte that you have been more successful in resolving propylenediamine than we have. Now I wish to ask you whether you would permit me to use the active propylenediamine in the investigation of compounds
>
> 
>
> $$\left[\begin{matrix} O_2N & \\ & Copn_2 \\ O_2N & \end{matrix}\right]X,$$
>
> of which we have already obtained five inactive series.

The Successful Resolution

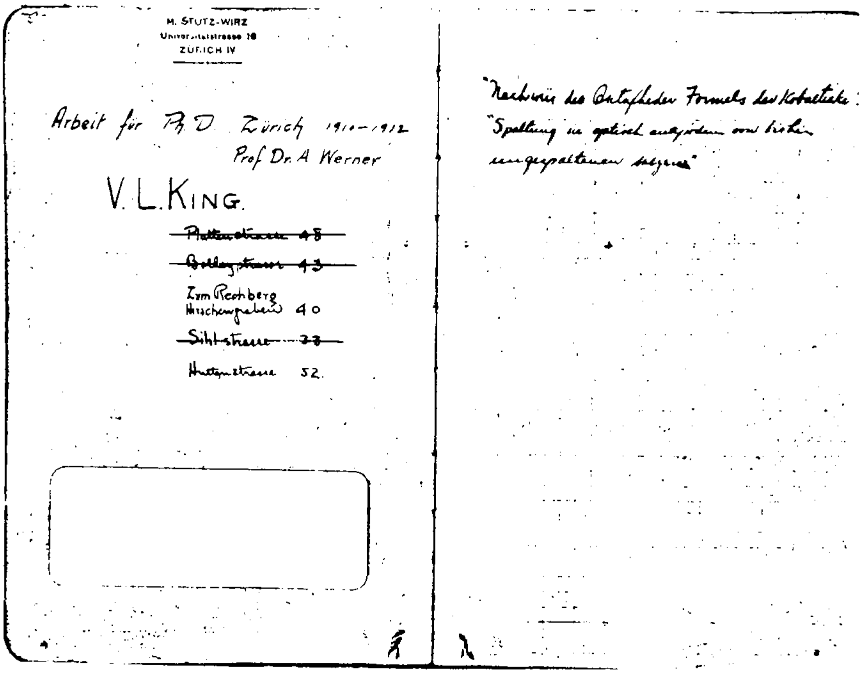
When Victor L. King arrived in Zürich, Werner assigned him the task of resolving carbonatobis(ethylenediamine)cobalt(III) bromide, which had been the object of at least one previous documented attempt at resolution. (Among the thousands of samples in the collection of Werner's complexes preserved at the Anorganisch-Chemisches Institut der Universität Zürich I found one labelled "Resolution experiment on



$$\left[\begin{matrix} & CO_3 \\ Co & \\ & en_2 \end{matrix}\right]Br$$

by means of silver *d*-tartrate, 20/I. 1908, Dubský). Under the date January, 1910 we find as the first entry in King's laboratory notebook (Fig. 3) the following:

Figure 2. Victor L. King (1886-1958), co-discoverer (1911) with Alfred Werner of optically active coordination compounds



M. STUTZ-WIRZ
Universitätstrasse 18
ZÜRICH IV

Arbeit für Ph D Zürich 1910–1912
Prof Dr. A Werner

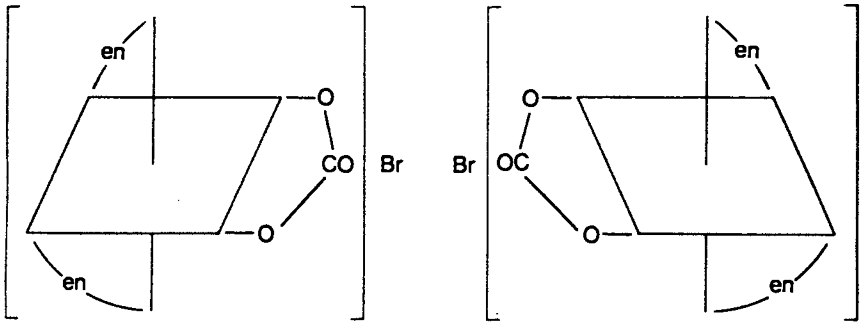
V. L. KING.

~~Plattenstrasse 48~~
~~Bolleystrasse 43~~
Zum Rechberg
Hirschengraben 40
~~Sihlstrasse 33~~
Huttenstrasse 52.

"Nachweis der Oktaeder Formeln der Kobaltiake:
"Spaltung in optisch aktiven von bisher
ungespaltenen Salzen"

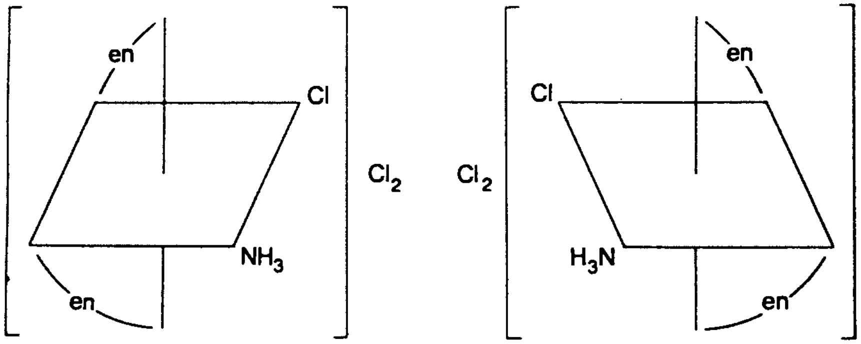
Figure 3

> The salt di-ethylenediamine carbonato cobalti bromide is usually represented as follows: [Coen$_2$CO$_3$]Br or



> The above salt molecule is not deckbar [superimposable] with its Spiegelbild [mirror image] and should consist of an equivalent mixture of optically active isomers. The object is to demonstrate the truth or fallacy of this and if possible separate the optically active isomers (20) (Fig. 4).

After a year's unsuccessful attempts to resolve this compound, King abandoned it and began work on a related compound, cis-chloroamminebis(ethylenediamine)cobalt(III) chloride, [Coen$_2$(NH$_3$)Cl]Cl$_2$:



> By removing Carbonato Group and placing 2 dissimilar groups NH$_3$ and Cl the vermutete undeckbarkeit [expected nonsuperimposability] of the spiegelbilder [mirror images] will be enhanced. By means of the camphor sulfonates perhaps these salts may be separated.

Werner's Privat-Assistent Ernst Scholze was simultaneously trying to resolve the corresponding bromo compounds--

cis-bromoamminebis(ethylenediamine)cobalt(III) salts, $[Coen_2(NH_3)Br]X_2$, for on Page 21 of King's notebook (undated, but sometime between April, 1911 and June 12, 1911) appears the statement: "With the Bromoamine Reihe [bromoammine series] the dextro salt falls right out and no fractionation is necessary. (Werner's Private Lab.)" By June 12, King had obtained the dextro diastereoisomer of his compound and shortly thereafter the levo diastereoisomer as well:

> I shall never forget the day that the optically active isomers were first attained. In connection with this work, I had been carrying out some 2000 fractional crystallizations and had been studying Madame Curie's work on radium for that purpose. After having made these 2000 separate fractional crystallizations which proved that the opposite ends of the system were precisely alike and that we had to do something more drastic, I proposed increasing the dissimilarity of the diastomers by using brom camphor sulfonic acid as a salt-forming constituent having extremely high optical activity. When this was tried, the isomers in the form of these salts literally fell apart (16).

King, who was accustomed to being greeted on the streets of Zürich with the inquiry, "Nun, dreht es schon?" (Well, does it rotate yet?), recalled how he walked into Werner's office with the long-awaited news. Werner "leaned back in his chair, smiled, and said not a single word." The tetrahedron had been forced to relinquish its monopoly on optical isomerism.

All Werner's students knew that something extraordinary had happened when Werner, who was known for his punctuality, did not appear at his five o'clock lecture. To everyone's astonishment, a young student announced that the lecture had been cancelled. Fearing that the antipodes might racemize overnight, Werner and King worked late into the night, making many derivatives and observing their rotations. Their fears, however, were unfounded, for the enantiomorphs proved to be remarkably stable.

Werner's excitement and pleasure were communicated not only to his students but touched many people, although indirectly. The late Peter Debye, then Professor of Physics at the University of Zurich, recalled:

> One early afternoon when I went from the lake to the Physics Institute after lunch, Werner hailed me from the opposite side of the Rämistrasse. It turned out that he wanted to talk to me about the fact that he had succeeded in making a coordination compound which showed rotation of the plane of polarization. I was very much interested indeed but did not quite understand why he talked to me, since we had had no

> scientific discussions at all before that time (21).

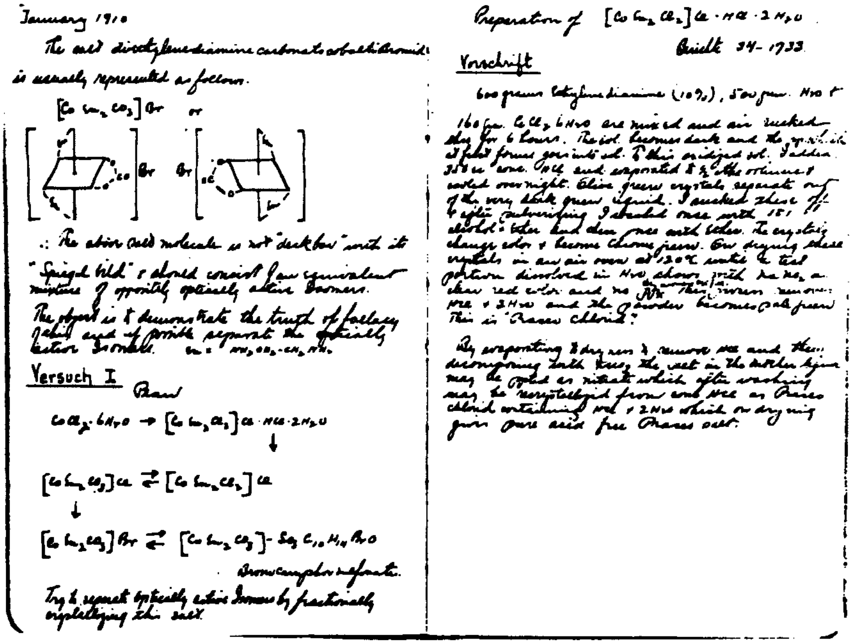
During that spring of 1911 many other persons must have been startled by the atypical and unusual behavior of Alfred Werner accosting casual acquaintances on the street to tell them the story of his greatest experimental triumph, a work which John Read, a former Doktorand of Werner's, called a "stereochemical achievement of the first order" (22).

In Werner's classic paper (23), which was received by the Berichte der Deutschen Chemischen Gesellschaft on June 24, 1911, little more than a week after King's success, Werner used stereochemical arguments reminiscent of van't Hoff's paper of 1874 on the asymmetric carbon atom. After citing several consequences of the octahedral hypothesis that are amenable to experimental verification, such as the occurrence of complex ions $[MA_5B]$ in only one form and the occurrence of complex ions $[MA_4B_2]$ and $[MA_4BC]$ in two isomeric series, Werner discussed a much more decisive proof—the existence of the optical isomers required by the octahedral model.

For his resolutions Werner had chosen the most widely used method, the racemic modification method developed by Pasteur. The method of diastereoisomer formation, although general in principle, often failed in practice, largely because naturally occurring optically active acids and bases are weak and their salts are not very stable in solution. In the same year in which the coordination theory was published, Kipping and Pope had synthesized the strong acids (+)-camphorsulfonic acid and (+)-bromocamphorsulfonic acid and thus had provided the stereochemist with a series of versatile resolving agents (24). It was the silver salt of the latter compound that brought Werner his widely acclaimed success. The process is illustrated schematically for King's salts (Figure 5).

Only the results of the first 39 pages (up to June, 1911) of King's work out of a notebook of 115 pages (up to 1912) were incorporated into Werner's publication, but most of King's work is included in his dissertation. King reported his results up to August 1, 1911 to Werner for use in Werner's lecture "Über optisch-aktive Kobaltverbindungen," delivered before the Schweizerische Naturforschende Gesellschaft at Solothurn, Switzerland that same day, but the lecture was not published. Thus the majority of King's work, including the resolution by means of the (−)-form of the resolving agent, the preparation of nine forms of the diastereoisomers, and syntheses of the optically active chlorides, nitrates, and sulfates has never appeared in the literature.

According to Werner, the investigation proved that "metal atoms can act as central atoms of stable, asymmetrically constructed molecules and that pure molecular compounds can also occur as stable mirror image isomers, whereby the difference between valence compounds and molecular compounds, which is still



January 1910

The salt diethylenediamine carbonatocobaltibromide is usually represented as follows.

$[Co\,en_2\,CO_3]Br$ or

∴ The above salt molecule is not "deckbar" with its "Spiegel bild" & should consist of an equivalent mixture of oppositely optically active isomers.

The object is to demonstrate the truth or fallacy of this and if possible separate the optically active isomers. $en = NH_2CH_2\text{-}CH_2NH_2$.

Versuch I

Plan

$CoCl_2 \cdot 6H_2O \rightarrow [Co\,en_2\,Cl_2]Cl \cdot HCl \cdot 2H_2O$

$\downarrow$

$[Co\,en_2\,CO_3]Cl \rightleftarrows [Co\,en_2\,Cl_2]Cl$

$\downarrow$

$[Co\,en_2\,CO_3]Br \rightleftarrows [Co\,en_2\,CO_3]\text{-}SO_3C_{10}H_{14}BrO$

Bromcamphor sulfonate.

Try to separate optically active isomers by fractionally crystallizing this salt.

Preparation of $[Co\,en_2\,Cl_2]Cl \cdot HCl \cdot 2H_2O$

Quelle 34-1733

Vorschrift

600 grams ethylenediamine (10%), 500 gm. H_2O &

160 gm. $CoCl_2\,6H_2O$ are mixed and air sucked thru for 6 hours. The sol. becomes dark and the ppt. which at first forms goes into sol. To this oxidized sol. I added 350 cc conc. HCl and evaporated to ½ the volume & cooled overnight. Olive green crystals separate out of the very dark green liquid. I sucked these off & after pulverizing I washed once with 1:1 alcohol: ether and then once with ether. The crystals change color & become chrome green. On drying these crystals in an air oven at 120°C until a test portion dissolved in H_2O shows with $NaNO_2$ a clear red color and no [illegible] This [illegible] removes HCl + $2H_2O$ and the powder becomes pale green. This is "Praseo chloride".

By evaporating to dryness to remove HCl and then decomposing with [illegible] the salt in the [illegible] liquor may be [illegible] as nitrate which after washing may be recrystallized from conc. HCl as Praseo chloride containing HCl + $2H_2O$ which on drying gives pure acid free Praseo salt.

Figure 4

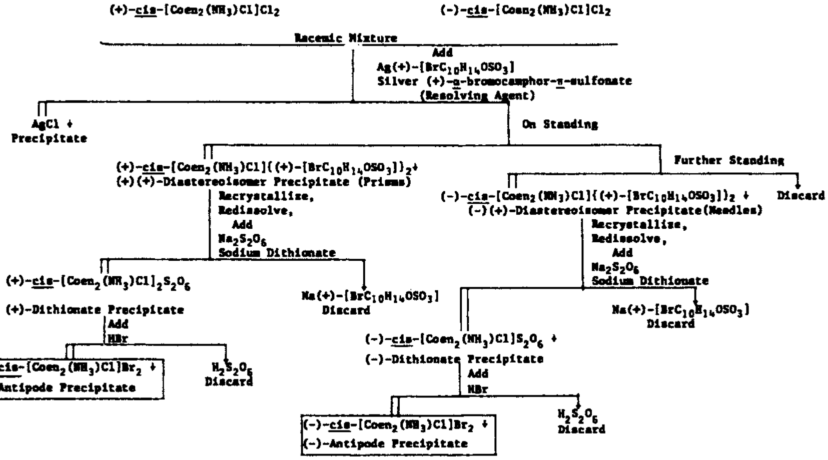


Figure 5. The first resolution of a coordination compound (simplified scheme)

frequently maintained, disappears entirely" (23). Moreover, it confirmed "one of the most far-reaching conclusions of the octahedral formula." In his doctoral dissertation (Figure 6), King considered the resolution to be "the last proof for the octahedral formula assumed by A. Werner" (25). He attributed the optical activity to mirror image isomerism rather than exclusively to the presence of an asymmetric atom. "Whereas until now only a few carbon compounds with such steric structure are known, a considerable number of such metal-ammines have already been successfully prepared" (25).

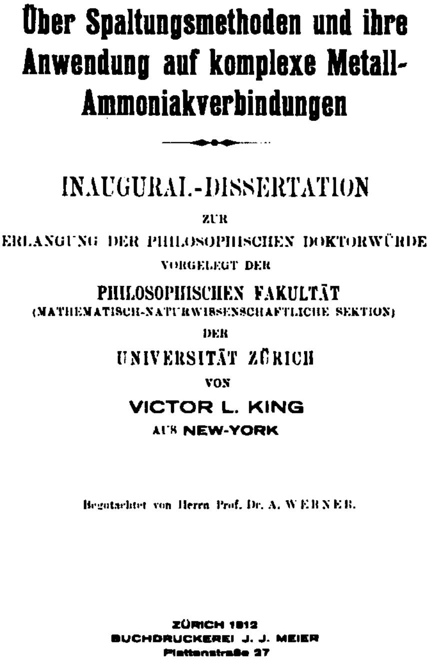
The resolution of optically active coordination compounds, a feat which "shook chemistry to its innermost foundations" (26), gained for the coordination theory the widespread recognition for which Werner had been striving so long. Nor was the theory's founder neglected, for two years later, largely in recognition of "the most brilliant confirmation of [his] stereochemical views" (27) as Lifschitz has described the resolution, Werner was awarded the Nobel Prize in chemistry.

Since Werner was originally an organic chemist with extensive experience in stereochemistry, the question as to why it took so long for him and his students to resolve coordination compounds successfully is an intriguing one to which no definite answer is available, but which has been a fruitful subject for speculation.

Although these speculations (28) have not yielded a definite answer to our question, perhaps they have persuaded us to rephrase it. Rather than asking what took Werner so long, maybe we should marvel that he succeeded at all in the time that he did. If we consider the possible variety of methods, complexes, resolving agents, instruments (Figure 7), and wavelengths as well as the highly specific experimental conditions sometimes required for success in such ventures, it is not unlikely that even for someone with Werner's chemical intuition and experimental skill, many years might be required to solve the problem. In the final analysis, Werner's conclusive proof of the octahedral configuration for cobalt(III) by the resolution of coordination compounds was made possible by his unshakable faith in his own ideas and his persistent and untiring efforts to prove them, even in the face of what might have seemed to others to be unsurmountable experimental difficulties.

Further Developments

"Whenever Werner opened up a new field, he expanded it with unbelievable speed" (26). This statement of Paul Karrer's was amply confirmed by Werner's investigations of optically active complexes, for once Werner had found the key to the resolution of complexes, a large number of articles describing additional resolutions appeared from his institute with great rapidity (29, 30). Within eight years, he and his students had resolved



Über Spaltungsmethoden und ihre Anwendung auf komplexe Metall-Ammoniakverbindungen

INAUGURAL-DISSERTATION
ZUR
ERLANGUNG DER PHILOSOPHISCHEN DOKTORWÜRDE
VORGELEGT DER
PHILOSOPHISCHEN FAKULTÄT
(MATHEMATISCH-NATURWISSENSCHAFTLICHE SEKTION)
DER
UNIVERSITÄT ZÜRICH
VON
VICTOR L. KING
AUS NEW-YORK

Begutachtet von Herrn Prof. Dr. A. WERNER.

ZÜRICH 1912
BUCHDRUCKEREI J. J. MEIER
Plattenstraße 27

Figure 6

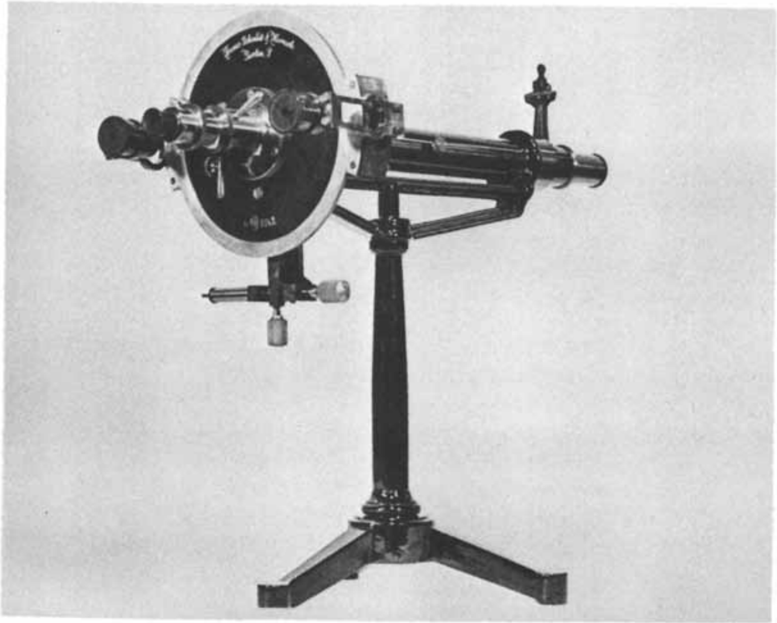
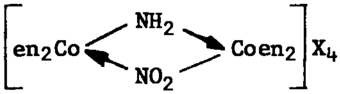


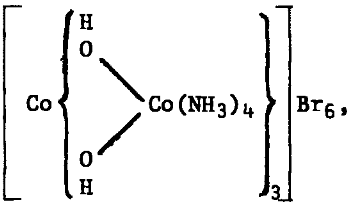
Figure 7. Werner's polarimeter (Franz Schmidt & Haensch model 8142)

more than forty series of cationic and anionic complexes, not only of cobalt but of other hexacoordinate transition metals as well. In this way he succeeded in proving octahedral configurations for iron(II), chromium(III), rhodium(III), iridium(III), and platinum(IV). In 1913 he even repaid his debt to Pasteur by using optically active inorganic octahedral complexes, which had been resolved by means of organic substances, to resolve in turn dimethylsuccinic acid, an organic tetrahedral compound (31). In the same year he also proved that polynuclear as well as mononuclear complexes could be resolved and thus demonstrated the theoretically predicted analogy between compounds containing two asymmetric carbon atoms and polynuclear complexes with two metal atoms, another striking confirmation of his octahedral hypothesis (32). In complete analogy with tartaric acid, which, in addition to the racemic (+)(-)- form, also exists in (+)- and (-)- enantiomers and in an internally compensated, nonresolvable (meso) form, Werner was able to demonstrate experimentally for the binuclear complex



the existence of a racemic (+)(-)- form, (+)- and (-)- enantiomers, and an internally compensated, nonresolvable (meso) form.

Although the compounds that Werner had resolved up to 1914 represented a remarkable variety of compound types, they all possessed one common characteristic—they all contained carbon. Because of the then prevalent view that optical activity was usually connected with carbon atoms, a number of Werner's contemporaries argued that the activity of all these compounds was somehow due to the ethylenediamine or bipyridyl molecules or to the oxalate ions contained in them, even though these symmetrical ligands are themselves optically inactive. In 1914 Werner was able to silence even the most sceptical of his opponents and to vindicate unequivocally his octahedral concept by resolving a completely carbon-free coordination compound of the $M(AA)_3$ type, viz., tris[tetraammine-μ-dihydroxo-cobalt(III)]-cobalt(III) bromide,



a compound that, ironically enough, had been first discovered by

Sophus Mads Jørgensen, Werner's primary scientific adversary (33).

In Werner's own words, the investigation proved that "carbon-free inorganic compounds can also exist as mirror image isomers" and that therefore "the difference still existing between carbon compounds and purely inorganic compounds disappears" (34). At last he had confirmed his long-held view of the unity of all chemistry. The structural theory of organic chemistry was only a special case of the coordination theory in which the carbon atom happened to have its valence equal to its coordination number. The last brick in the crumbling wall of separation between inorganic and organic chemistry had been razed. The demolition begun eighty-six years earlier by Friedrich Wöhler with his artificial synthesis of urea from ammonium cyanate had been completed by Alfred Werner.

During his last years Werner devoted himself almost exclusively to studies of the optically active compounds which had brought him the Nobel Prize and had proved beyond the shadow of a doubt his stereochemical views. His investigations of the optically active coordination compounds of cobalt, chromium, iron, rhodium, iridium, and platinum underlie much of the more recent and sophisticated studies of the thermodynamics; kinetics; visible, ultraviolet, and infrared spectra; rotatory dispersion; circular dichroism; ligand exchange; racemization; and absolute configuration of these and similar compounds.

The validity of Werner's structural views was later amply confirmed by numerous X-ray diffraction studies. Yet, despite the introduction of more direct modern techniques, his classical configurational determinations by simple indirect methods still remain today a testament to his intuitive vision, experimental skill, and inflexible tenacity. Although some of his methods of resolution have been improved and his specific rotation values for many complexes have been shown to be too low, we must remember that he was the pioneer who first opened the door to a previously unsuspected field. In his last works, he stood on the threshold of an extremely complicated research area--the investigation of optically active coordination compounds containing optically active ligands. Had the powerful, creative trend of his life not been cut short by his untimely death, there is no telling what Alfred Werner might have accomplished in this field.

Acknowledgments

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11

The Evolution of Stereochemical Concepts in Pharmacology

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The purpose of this paper is to examine the historical development of the application of stereochemical concepts to the field of pharmacology. It is not possible, however, to present an exhaustive treatment of so broad a subject within the confines of the present paper, and thus it will be necessary to focus the discussion on selected aspects of the topic. Particular attention will be devoted to the attempts to explain the observed difference in activity between optical enantiomers (compounds which are non-superimposable mirror images of each other).

The study of the stereochemical factors involved in drug action developed out of an attempt to explain the mechanism of drug action in chemical terms. Although the iatrochemists of the seventeenth century had already attempted to relate the physiological action of certain substances to their chemical properties (especially acidity and basicity), chemistry and pharmacology had not developed sufficiently enough to allow for significant advances in this direction before the nineteenth century. The first serious attempt to relate chemical composition to physiological action in a systematic manner seems to have been made by James Blake, an English physician who later emigrated to America. In 1839, Blake showed that the different salts of a given metal tended to produce the same physiological effect, thus indicating that the metallic element of the salt seemed to be largely responsible for its activity. He later found that elements which were isomorphic generally had similar pharmacological properties. Blake's work demonstrated that a relationship could be established between the pharmacological action and the chemical nature of a substance (1,2).

While structural organic chemistry was still in its infancy in the 1860's, some attempts were made to relate the physiological action of certain organic compounds to their chemical structure. These early studies understandably concentrated largely on relating physiological activity to the presence of certain elements or functional groups in a molecule, not on more complicated questions involving the general structure or the stereochemistry of the

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molecule. Thus Benjamin Ward Richardson, the British physician and physiologist, attempted to assign specific pharmacological properties to certain functional groups (e.g., he associated the nitrite group with vasodilation and quickening of the heart) (1, 2).

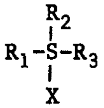
Probably the most influential of these early studies on structure-activity relationships was the investigation of alkaloids and amines by two Edinburgh scientists, Alexander Crum Brown, the chemist, and Thomas Fraser, the pharmacologist, beginning in 1867. They clearly recognized that the constitution or structure of a molecule was as important as its chemical composition in explaining biological activity (e.g., two isomers may have very different physiological properties), but unfortunately the structures of most organic drugs and poisons were not known. Although the exact structures of many of the compounds they studied were unknown, they were able to establish a relationship between a specific structural feature of a molecule and a particular pharmacological property. Brown and Fraser demonstrated that the quaternary ammonium salts of various alkaloids (such as strychnine and morphine) and of various amines always seemed to be associated with a paralyzing action similar to that of curare. They attributed this action to the presence of a pentavalent nitrogen atom in all of these substances (1,2).

The work of Brown and Fraser stimulated interest in the application of structural organic chemistry to pharmacology and encouraged research on structure-activity relationships. It is also of significance in our present discussion because it led to one of the early examples of the attempt to take stereochemical factors into account in considering drug action. In 1872, Brown and Fraser extended their work on nitrogen compounds to show that sulfonium salts possess the same paralyzing properties exhibited by quaternary ammonium compounds (3). The studies of other investigators soon revealed that arsonium, phosphonium and stibonium salts all exhibited a curare-like action (4,5,6). In other words, the nature of the central atom in the onium salt, whether nitrogen, arsenic, sulfur, etc., did not seem to affect the pharmacological properties of the compound. The paralyzing action seemed in some way to be associated with the whole structure of these onium compounds.

At the close of the nineteenth century an understanding of the stereochemistry of elements other than carbon began to emerge. In the 1890's for example, Alfred Werner and his co-workers investigated the stereochemistry of nitrogen compounds (7). William Pope and Stanley Peachy established in 1900 that the asymmetric quadrivalent sulfur atom acts as a center of optical activity (8). Chemists and pharmacologists began to associate the paralyzing properties possessed by onium salts with the change from a planar structure to a three-dimensional structure (9,10,11). For example, it was argued that the molecule

$$R_1-S-R_2$$

must have a planar configuration, since there are only three groups involved. A sulfonium salt of structure



$$\begin{array}{c} R_2 \\ | \\ R_1-S-R_3 \\ | \\ X \end{array}$$

must, however, have a tetrahedral configuration, since such compounds possess optical activity when four different groups are attached to the sulfur atom. No explanation was offered as to exactly why this change from a planar to a three-dimensional configuration resulted in the introduction of paralyzing properties, but it was generally assumed that this alteration in the stereochemistry of the molecule was somehow responsible for the development of curare-like effects.

H. R. Ing and his associates were to show many years later that the curare-like action of onium salts was actually due to their ionic character (12). They apparently act, as does curare, by antagonizing acetylcholine (itself a quaternary ammonium compound) by competing for the receptor site. The possibility that the action of quaternary ammonium salts might depend upon their strong basicity was suggested early in the century (12), but this view does not seem to have been widely accepted before Ing's work. Thus this "classic" case which was frequently pointed out in the early twentieth century as an example of the importance of stereochemistry for pharmacology turned out to depend upon an ionic effect rather than upon a stereochemical effect.

Other examples of the importance of stereochemical effects in the action of certain drugs also came to light in the late nineteenth and early twentieth centuries. For example, in the 1890's the geometric isomers maleic and fumaric acid were shown to differ significantly in their toxicity towards various microorganisms (13,14,15). Other examples of differences in pharmacological activity among geometric isomers were later uncovered (16,17).

Geometric isomerism, however, never received nearly as much attention from pharmacologists and medicinal chemists as did optical isomerism, probably because so many interesting and important drugs, especially the alkaloids, existed in optically isomeric forms. In addition, optical isomers probably had a certain theoretical appeal, since they seemed to be essentially identical in their physical and chemical properties; hence, it was a difficult challenge to explain differences in physiological activity.

The fact that optical isomers may differ in their biological effects had been known since about 1860 when Louis Pasteur demonstrated that certain microorganisms preferentially destroy one member of a pair of optical isomers over the other. These studies were later extended by others to show that this differentiation also applied to oxidation by animal tissues. Other observations revealed that certain ferments could distinguish between optical isomers, and that optical isomers may differ in taste. It thus became clear that living organisms could, at least in some cases, distinguish between enantiomers (18,19).

A number of attempts were made in the late nineteenth century to compare the pharmacological and toxicological properties of pairs of optical isomers, but the first convincing examples of differences in pharmacological activity between enantiomers was provided by the work of Arthur Cushny. I have already discussed Cushny's work on this subject in some detail in a previous paper presented before the Division of History of Chemistry (20), and here I will just briefly review the material most pertinent to our present discussion.

In the period from 1903 through 1909, Cushny (who began his work on optical isomers at the University of Michigan and later continued it at London and at Edinburgh) demonstrated that one member of a pair of optical isomers could in some cases exhibit a much greater pharmacological activity than its mirror image. For example, ℓ-hyoscyamine appeared to be twelve to fourteen times as potent as d-hyoscyamine with respect to their action on the motor nerve endings (21,22,23,24).

In the rest of this paper, I would like to focus on the attempts to explain this phenomenon, for this difference in activity of optical isomers was a clear example of how the spatial arrangement of the atoms within a molecule could influence its pharmacological effects. It helped to stimulate pharmacologists and medicinal chemists to take stereochemical factors into account in considering drug action.

We should begin by asking how Cushny himself interpreted the results of his work on optical isomers. It is interesting to note that he did not really emphasize the stereochemical configurations of the molecules, and that he placed more emphasis on physical properties than on chemical structure. Before discussing his views, however, I must provide some brief background about theories of the mechanism of drug action at the turn of the century.

In the early part of the twentieth century there was considerable discussion and controversy over the question of whether physical (or perhaps it would be better to say "physicochemical") or chemical properties played more of a part in determining drug action. I have discussed this subject in more detail elsewhere (25). Although it was recognized that both chemical and physical factors were probably involved to some extent, and that one could not always clearly distinguish between them, there was a tendency among pharmacologists and others concerned with the question of drug action to emphasize one or the other approach. The supporters of the chemical viewpoint held that drugs generally exerted their effects by forming a chemical union with the cell or with some component of the cell. This view received its clearest exposition in the receptor theory developed by John Newport Langley in England and by Paul Ehrlich in Germany. Ehrlich emphasized that for a drug or poison to act on a cell, it must possess a specific group of atoms which have a specific affinity for and can combine with another group of atoms on a chemical side chain of the protoplasmic molecule, so that it can be fixed or anchored in the cell (26). Supporters of the physical or physicochemical viewpoint, on the other hand, argued that drugs did not generally unite chemically with the cell, but rather induced their effects by altering the surface tension, electrolytic balance, osmotic pressure, etc. of the cell (25).

While Cushny recognized that both physical properties and chemical reactions can play some part in pharmacological action, he gave much more emphasis to the former in his writings (25). It is not surprising then that his theory of the action of optical isomers reflects this bias. Yet he had to admit that a chemical reaction was in some way involved in the ability of organisms to distinguish between enantiomers, for enantiomers have identical physical properties (except for the direction in which they rotate the plane of polarized light). So Cushny postulated that the two optical isomers combined with an optically active receptive substance in the cell, probably an acid or a base, to form two diastereomers (stereoisomers which are dissymmetric, at least in part, and hence are not mirror images of each other). So, for example, if the receptive substance was levorotatory, the reaction would be as follows:

d - isomer + ℓ - receptor = d - isomer - ℓ - receptor

ℓ - isomer + d - receptor = ℓ - isomer - d - receptor

The two diastereomeric products differ in their properties, of course, since they are not mirror images, and Cushny argued that it is the difference in physical properties, such as solubility, of these diastereoisomers which leads to their difference in pharmacological activity (27,28,29).

Note that while Cushny admitted the involvement of a chemical reaction, he emphasized that it was the difference in physical properties of the compounds formed by the reactions which determined the difference in pharmacological activity. In all of his discussions on the subject, he emphasized the difference in optical rotation between two enantiomers, rather than speaking of their different configurations. Structural formulas play almost no role in his treatment of the subject. In fact, he separated out the influence of the asymmetric carbon atom from that of the general configuration or structure of the molecule (20).

Cushny specifically rejected the possiblity that the difference in pharmacological activity of two enantiomers might be due to a difference in their ability to combine with the receptor. It was true, he stated, that some chemical reaction occurred between the drug and the receptor, but this followed whether the d-isomer or the ℓ-isomer was present. He added that the "difference in action lies not in the facility with which the chemical combination is formed, but in the physical characters of the resultant compound" (29). Perhaps Cushny found it difficult to imagine that the receptor could differentiate between two substances so identical in structure as optical enantiomers.

It must be remembered that in the early twentieth century, chemical reactions were thought of largely in terms of covalent and ionic bonds. Concepts of hydrogen bonding, van der Waals forces, etc. had not yet been developed, nor had an understanding of the secondary and tertiary structure of proteins and other macromolecules yet emerged. I find that the pharmacological and pharmaceutical chemical writings of this period still tend to be largely concerned with two-dimensional chemistry. Chemical interactions were thought of largely in terms of the reaction of a specific functional group on one molecule with a specific functional group on another molecule, although admittedly the term "chemical" was beginning to be interpreted more broadly by some (the question of whether relatively nonspecific processes such as adsorption might involve chemical forces as well as physical forces was, for example, being discussed) (25).

Some investigators in the early twentieth century did attempt to explain the difference in activity between enantiomers in terms of the stereochemical configurations of the drug and the receptor, but these early attempts were rather vague. The chemist Alfred Stewart, author of a 1907 book on Stereochemistry, argued that spatial or three-dimensional factors play a part in many chemical reactions involved in vital processes. He suggested that the speed of reaction of an optically active drug with an asymmetric tissue substance sometimes depends upon the spatial arrangements of the atoms (30). Stewart noted that it was probable that the tissues, which are themselves asymmetric, select the substances whose stereochemical configurations best fit in with their own (18), a view which reminds one of Emil Fischer's well-known "lock and key" analogy for the reaction between an enzyme and its substrate. Stewart did not, however, suggest any specific mechanism which could explain how the tissues were able to "select" one optical isomer in preference to another.

The dependence of the pharmacological action of a molecule upon its stereochemistry was stressed by others such as the German medicinal chemist Sigmund Fränkel, who argued that the orientation of the atoms or radicals of a molecule in space is at least as important as their chemical nature in determining physiological activity (31). Suggestions as to the mechanism of action involved, however, did not really go beyond the "lock and key" analogy, or, as one pharmacologist suggested, a "glove and hand" analogy (i.e., just as the glove from the left hand cannot fit the right hand, so perhaps an ℓ-isomer could not "fit" a d-receptor) (32).

No satisfactory three-dimensional explanation as to how a receptor could distinguish between optical isomers seems to have been offered until 1933. In that year, Leslie Easson and Edgar Stedman of the Department of Medicinal Chemistry at the University of Edinburgh expounded an alternative to Cushny's theory (33). They criticized Cushny for considering optical activity to be a factor which was quite distinct from general structure in determining the magnitude of the specific pharmacological activity of the molecule, a view which they believed was commonly held. They felt that the difference in activity between optical isomers, just as the difference in activity between any two different substances, depended upon their molecular arrangement, and suggested a specific mechanism which could explain the difference. Easson and Stedman assumed that three of the four groups surrounding the asymmetric carbon atom of the drug are involved in the reaction with the receptor. For the drug to produce the maximum physiological effect, they hypothesized, it must be attached to the receptor in such a way that groups B, C, and D (Figure 1) in the drug coincide with B', C', and D' on the receptor. This alignment can be achieved by only one of the enantiomers, and hence one enantiomer would exhibit greater activity than the other.

They reasoned that if their theory were correct, i.e., if it were not optical activity per se but the general structure of the molecule which was important in determining pharmacological activity, than a molecule such as V (Figure 1), which has the same configuration of the three binding groups as does the active isomer III, should have about the same activity as the active isomer even though V is optically inactive (it does not contain an asymmetric carbon atom). They recognized, however, that one would have to take into account any changes in the physical properties of the molecule associated with the substitution of B for A. Changes in the solubility of the molecule, for example, could significantly alter its pharmacological activity.

Easson and Stedman offered evidence from the literature and from their own experimental work to support their views, and I will just mention one example. Compound VII (Figure 2) contains an asymmetric carbon atom and hence exists in two optically active forms. One of these, the ℓ-isomer, possesses exceptional miotic activity (i.e., it constricts the pupil of the eye), five times that of the corresponding d-isomer. Compound VIII, if R is a hydrogen atom, possesses very little miotic activity. The introduction of a methyl group into compound VIII, converting it to VII, thus greatly increases the miotic activity, while at the same time introducing an asymmetric carbon atom into the molecule.

One might be tempted to associate this increased activity with the optical asymmetry. Suppose, however, postulate Easson and Stedman, that the drug (VII) is attached to the receptor by the amide and the amine groups (both of which are necessary for activity), and that in the more active isomer the methyl group causes a more perfect combination to take place between the drug and the receptor than would occur in its absence. In the less active isomer, however, the methyl group would be directed away

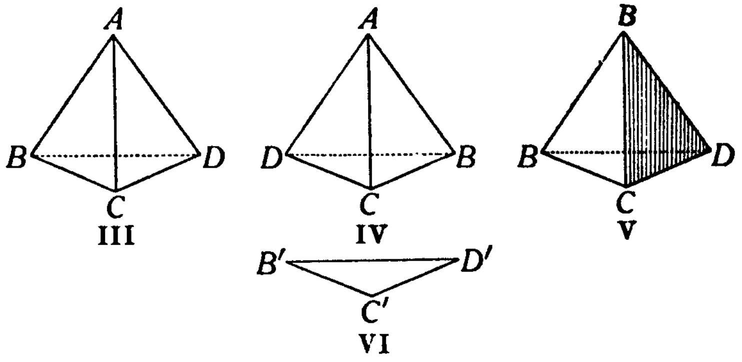


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Figure 1. Diagrammatic representation of "three-point contact" theory from 1933 paper of Easson and Stedman (33)

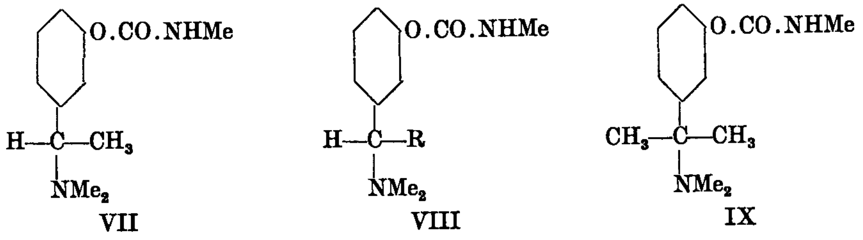

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Figure 2. Chemical formulas from Easson and Stedman paper (33)

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from the receptor and could not directly influence the fixation of the drug. If this were the case, then one would expect, first of all, that the less active isomer would have about the same activity as VIII (where R is a hydrogen atom), since the methyl group is not in a position to influence the fixation of the drug; and, secondly, that if the hydrogen atom attached to the asymmetric carbon atom in VII were replaced by a methyl group, the resulting product (IX) should have about the same miotic activity as the active ℓ-isomer of VII, even though IX is optically inactive. Their own experimental studies on these compounds tended to support their hypothesis, although the results were not clearly definitive.

I should note that Easson and Stedman indicated that it was not necessary for each of the three groups involved in fixing the drug to actually combine chemically with the receptor, but that in many cases one or more groups might merely cause a better "fit" of the drug to the receptor (rather than being linked to the receptor through "normal valencies") (33). H. R. Ing of Oxford, however, criticized Easson and Stedman in 1937 for introducing the vague notion of "fit," which he felt was unnecessary. Ing admitted that the stereochemical configurations of the drug and the receptor are important, but he felt that these factors could be included under Cushny's explanation. The different physical and chemical properties of the diastereomeric drug-receptor compounds of Cushny's theory, Ing noted, are presumably based upon the mutual spatial arrangements of the drug and the receptor in the compound formed by them (34). Ing's criticism of the concept of "fit" may seem at first inconsistent with his own statement in 1935 that: "The conception of fit between drug molecules and the tissues on which they act appears to the author to be fundamental to any general theory of how drugs act." This statement, however, was followed by the remark that "the hypothesis of fit between drugs and tissues is at present infertile" because "nothing is known of the nature of the receptors on which drugs are supposed to act" (35). Presumably Ing's criticism of the Easson-Stedman hypothesis was based on this feeling that such theories were at the time sterile, and on the fact that Cushny's hypothesis could encompass "fit" if one assumed that the physical properties of the drug-receptor compound depended upon the "fit" between the drug and the receptor.

A few years later, in 1943, Ing had to admit that Cushny's view was hard to reconcile with the receptor theory as developed by A. J. Clark in the 1930's. Under Cushny's view, both isomers combined with equal facility with the receptor, but the two drug-receptor compounds had different properties and therefore were not equally effective pharmacologically. If this were the case, however, the less active isomer should antagonize the action of the more active isomer, because it would compete on equal terms for the available receptors but would form a less active compound. The experimental evidence indicated, however, that optical isomers generally did not antagonize each other but acted additively. If one accepts the receptor theory, Ing noted, then the difference in activity of optical isomers must be presumed to depend upon the ease with which each isomer combines with the receptor, with both isomers forming equally effective drug-receptor compounds. In that case, one would not expect antagonism between the isomers.

He went on to add that this conclusion appears remarkable. Ing apparently found it hard to imagine, in spite of the fact that he knew of the Easson-Stedman theory (which he did not mention in the 1943 paper), that the receptor could differentiate between two molecules as identical in structure as optical isomers. In the case of stereoisomers which are not optical enantiomers, however, he felt that it was quite reasonable to expect that their ease of combination with the receptor is determined by their stereochemical configuration (36).

Ing's reaction may well typify the initial general response to the hypothesis of Easson and Stedman. It does not seem to have received widespread attention or acceptance until about 1950, when suddenly the "three-point contact theory" (essentially the Easson-Stedman model) found general favor in pharmacology and biochemistry. Some discussion of the theory, and evidence for or against it, did appear in the literature in the 1930's and 1940's (34,37, 38,39), but it apparently did not excite general interest or enthusiasm. In addition to conflicting evidence concerning the Easson-Stedman view, I would suspect that its slow acceptance was also partly due to a factor suggested by Colin Russell in his paper at this symposium with respect to the "puckered" ring model for cyclohexane. He suggested that the question of the conformation of the six-membered ring may have been largely irrelevant to what most organic chemists were doing in the first half of the twentieth century. In a similar way, I think that the Easson-Stedman model was in many ways "irrelevant" to the problems tackled by pharmacologists and medicinal chemists of the 1930's and 1940's. Their attention was focused on the synthesis of new drugs and on investigations to determine the site and general mode of action of both old and new drugs. There was still much to be done at the organism and organ level in terms of the understanding of drug action, and theories at the molecular level were rather speculative (and difficult to prove or disprove) and largely incapable of application to the practical problems faced by pharmacologists and medicinal chemists in that period (recall Ing's comment that the concept of fit was "infertile" in 1935).

It is interesting to note that beginning in 1935 Max Bergmann and his co-workers developed a similar theory for enzymes, postulating that for an enzyme to differentiate between two enantiomeric substrates it must contain three or more atoms or atomic groups, fixed in space with respect to one another, which enter into combination with a similar number of groups on the substrate (forcing the latter into a fixed spatial position) (40,41). They do not refer to Easson and Stedman in their work. The "polyaffinity theory" of Bergmann, however, also does not seem to have received widespread attention at the time. It was not until A. G. Ogston developed a similar theory in 1948, as we shall see, that the "three-point contact" theory of enzyme action made a significant impact on biochemistry, thus paralleling the situation in pharmacology.

In the late 1940's and early 1950's, the three-point contact theory began to appear in a number of guises to explain the action of certain enzymes, drugs, hormones, etc. It is not completely clear as to why this hypothesis, which was essentially the view suggested by Easson and Stedman in 1933, suddenly came into prominence around 1950. No doubt an improved understanding of chemical bonding and of stereochemistry played a significant role.

Certain work in biochemistry and pharmacology had also led to a heightened concern with three-dimensional factors in drug action by this time. The recognition in the early 1940's, for example, that sulfanilamide competes with p-aminobenzoic acid, a natural metabolite, because of their similar architecture helped to focus attention on the importance of molecular size and shape in determining drug action (42,43). In 1946, F. W. Schueler demonstrated the importance of the distance between the hydroxyl or keto groups of estrogens in determining their relative activity (44). Two years later, Carl Pfeiffer commented:

"Attempts to correlate structure-activity-relationships (SAR) of chemical series of pharmacological importance have hitherto mainly considered activity as variations in chain length of aliphatic series as drawn in two dimensions. Occasionally theories have been centered around the well-known ring systems of organic chemistry. Greater correlation and understanding of SAR might be obtained by depicting formulas in three dimensions, with bond distances calculated as accurately as our present knowledge will allow" (45).

Pfeiffer then applied his suggestion to a study of muscarinic drugs (drugs which simulate the effects of parasympathetic nerve stimulation), calculating the distances between the three "prosthetic" chemical groups which he believed were responsible for muscarinic activity, and relating these interprosthetic distances to pharmacological activity (45).

In that same year, 1948, A. G. Ogston of Oxford University introduced a hypothesis similar to that of Easson and Stedman in an attempt to explain how an enzyme could produce an asymmetric product from a symmetrical reactant. Ogston was apparently unaware of the Easson-Stedman theory, or at least he made no mention of it in his short paper. Nor did he mention the previously noted "polyaffinity theory" of Max Bergmann and his colleagues. His own concept developed out of a consideration of two metabolic studies utilizing isotopic tracers in which the investigators had concluded that certain compounds could not be intermediates because they were symmetrical molecules and the products formed were asymmetric. Ogston pointed out, however, that it was entirely possible that an enzyme could distinguish, for example, between the two supposedly identical carboxyl groups in amino-malonic acid. If a three-point combination is involved between the enzyme and the substrate, he postulated, then it is conceivable that decarboxylation might take place only at site a' (Figure 3) or only at site b', since they are catalytically different. The product produced would then be asymmetric (46).

The similarity of the Ogston hypothesis to the Easson-Stedman model is obvious. The Ogston hypothesis soon became widely accepted in biochemistry and probably helped to pave the way for the adoption of a similar view for drugs by pharmacologists (47,48,49).

The three-point contact theory was utilized shortly thereafter (1950) by Ogston's colleague at Oxford, H. K. F. Blaschko, to explain the difference in activity between the two optical isomers of the hormone adrenaline (which had been demonstrated by Cushny). Blaschko, after describing the three-point contact theory of enzyme action (but without specifically mentioning Ogston), stated that:

"The adrenaline molecule has an asymmetric carbon atom; its laevorotatory isomer, which occurs in nature, is highly active. We shall therefore assume that three of the groups attached to the asymmetric carbon atom are essential in the reaction with the excitable tissue. We assume that these three groups are:

(a) the catechol group,
(b) the group $-CH_2 \cdot NH \cdot CH_3$, and
(c) the hydroxyl group.

These three groups are assumed to be arranged in a fixed spatial relationship relative to the tissue receptors. We might say: the tissue receptors for adrenaline have three receptacles or anchorages, one for each of these groups.

The stereochemical specificity of the action of adrenaline differs from that of the enzyme discussed above; the specificity is not absolute: dextro-adrenaline has about 1/12 to 1/15 of the action of laevo-adrenaline on the arterial blood pressure. How can this be explained? It is obvious that dextro-adrenaline cannot attach itself in the same way to the receptors as laevo-adrenaline. We must assume that one of the three receptacles is not engaged: the dextro-adrenaline molecule is attached by the basic group and by the catechol group; the hydroxyl group is not engaged. The receptacle for the hydroxyl group is faced by the hydrogen atom attached to the asymmetric carbon atom. The dextro-adrenaline molecule is therefore held in two points; this attachment is less firm; the dextro-adrenaline molecule has a greater degree of freedom on the receptor and is therefore less active" (50).

Blaschko made no reference to the hypothesis of Easson and Stedman. At about this same time, the three-point contact theory was used by R. L. Wain and his associates to account for differences in activity between optical enantiomers of certain plant growth-regulating substances (51,52). Unlike Blaschko, Wain and his co-workers specifically refer to the earlier work of Easson and Stedman (51).

As one final example of the widespread interest in the three-point contact theory in the early 1950's, I will mention the application of the theory to explain differences in activity among optical isomers of various synthetic analgesics by A. H. Beckett of the School of Pharmacy of Chelsea College of Science and Technology. Beckett, who has contributed significantly to our knowledge of the stereochemistry of drug action in the past two decades, utilized the diagram shown in Figure 4 in a 1954 article on synthetic analgesics (coauthored by A. F. Casy). In all of these compounds the tertiary basic group and the aromatic ring seem to be essential for activity, so Beckett and Casy assumed that they are involved in the drug-receptor interaction. The third group (X), a hydrocarbon moiety, forms a third point of interaction with the receptor surface and hence helps to promote the formation of the drug-receptor complex. It can only be in the right position to become involved in the interaction, however, in one of the two enantiomers, in this case the (-)-isomer. Hence the (-)-isomer is more active than the (+)-isomer (53). In 1955, Beckett and Casy published a general review article on "Stereoisomerism and Biological Action," a paper in which they refer to the Easson and Stedman paper of 1933 for the first time (54).

By the mid-1950's, the three-point contact theory of drug action seems to have become well established as a mechanism of explaining differences in biological activity among optical enantiomers. By 1951, H. R. Ing (probably influenced by the work of his Oxford colleagues Ogston and Blaschko) had fully accepted this view (55).

There have, of course, been many advances in the understanding of the stereochemistry of drug action in the past twenty years. It is now clear, for example, that stereospecificity can be explained on the basis of a one-point or two-point contact theory as well as a three-point contact hypothesis (56,57). The influence of conformation on drug action has become a subject of investigation as stereochemical studies increase in sophistication I shall leave the discussion of recent work, however, to the chemists. I have tried to provide some insight into the impact that stereochemistry has had on pharmacology over the past hundred years, but my paper has presented only a broad outline of this complex subject. There are many details which will have to be filled in by further research into the history of chemical pharmacology.

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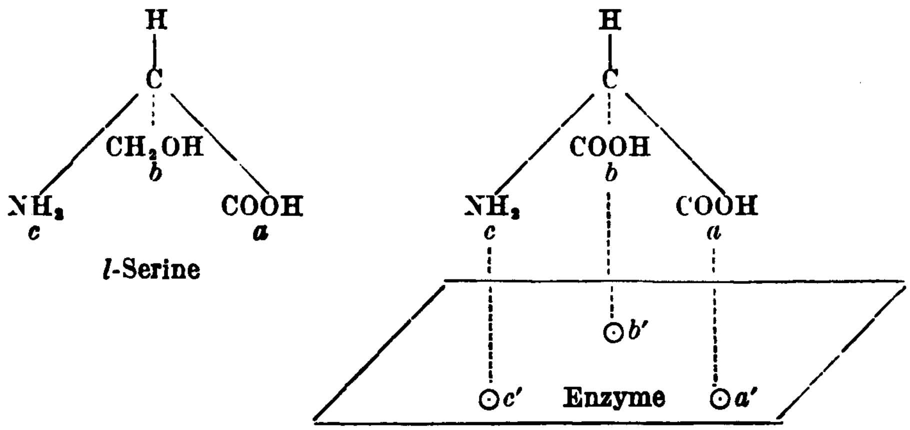
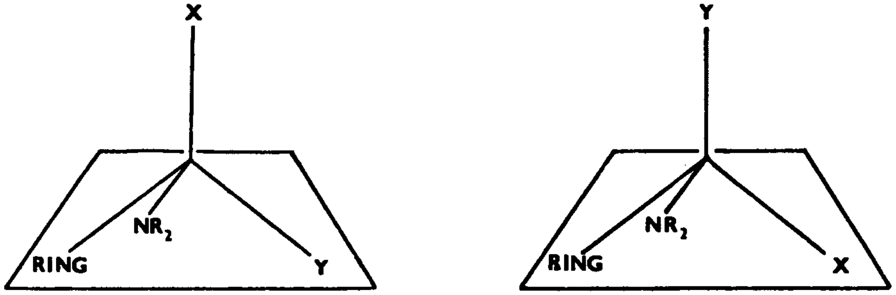


l-Serine

Amino-malonic acid

Nature

Figure 3. The Ogston hypothesis (46)



(+)– isomer

(–)– isomer

Journal of Pharmacy and Pharmacology

Figure 4. Diagram of Beckett and Casy representing the action of synthetic analgesics (53)

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12

The Origins of Conformational Analysis

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1. The Major Landmarks

The concepts of conformational analysis have so deeply penetrated into the fabric of theoretical organic chemistry that it is difficult to realise that, in some respects at least, the subject is not yet a quarter-century old. The terms "conformation analysis" (1) and "conformational analysis" (2) occur in the early 1950s, but it was Barton's classic paper (3) on "The Conformation of the Steroid Nucleus" (1950) that is generally regarded as launching the subject. In 1956 he and Cookson reported:

> "In the last five years the importance of the existence of preferred conformations in organic chemistry has become widely recognised under the title of 'conformational analysis'" (4).

The magnitude of Barton's achievement in this field has been widely - and rightly - recognised. But it must not be allowed to blind us to the importance of events preceding 1950, what we might call the pre-history of conformational analysis. Few, if any, scientific concepts appear, like Minerva, fully-formed in the brain of their creator, and most have their origins traceable in earlier scientific writings. Conformational analysis is no exception, and the development of its rudimentary ideas may have something to tell us about scientific growth in general. Certainly it presents several features of remarkable interest.

At the very heart of present thinking about conformational analysis lie several basic assumptions. Two are of fundamental importance:

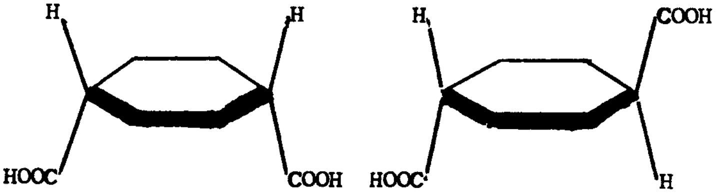
(a) The recognition of rotational energy-barriers for carbon-carbon single bonds, with preferred relative arrangements of substituent groupings.

(b) The postulation of so-called "strainless rings".

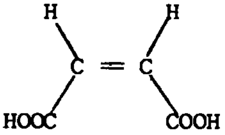
In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

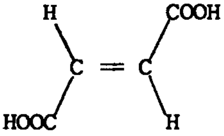
The next paper deals with an aspect of the first, and my purpose is to draw attention to the strange history of the second. In a recent paper (5) Prof. Ramsay has given a valuable synopsis of the course of events in the late 19th and early 20th centuries, while Prof. Eliel has chronicled the period 1950-1973 (6). It would be presumptuous for me to try to reproduce their work. Instead, I shall give a brief indication of the principal milestones in the journey to 1950, and shall then offer a tentative analysis of the curious story that emerges.

As a point of departure we may take the famous paper by Hermann Sachse "On the geometrical isomers of hexamethylene derivatives" (7). Baeyer had reported two forms each for hexahydromellitic acid (8) and hexahydroterephthalic acid (9). These had been explained in terms of planar rings (10), e.g.



and by their analogy with maleic and fumaric acids





had been designated respectively "maleinoid" and "fumaroid". The ready interconversion of the two forms of each acid caused Sachse to question the rigidity of the 6-membered ring and (by implication) the analogy with the unsaturated acids. He pointed out that Baeyer's insistence on a slightly strained planar ring for cyclohexane was not strictly necessary. Given a regular tetrahedral disposition for all valencies of the ring carbon atoms one could alternatively postulate two arrangements, each quite free from strain. The one he designated "normal" would have its atoms in a zig-zag pattern, and this would be symmetrical and relatively rigid. The other form would be less symmetrical and more flexible.

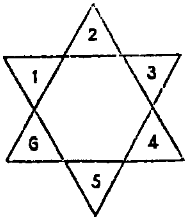


Figure 1. Sachse's representation of "normal" cyclohexane

Apart from an "end-on" view of the "normal" form (Fig. 1), Sachse did not depict these primeval "chairs" or "boats" but did offer instructions for constructing models of them out of cardboard tetrahedra. They were in fact derived from an earlier suggestion he had made for models of the benzene molecule (11). A more detailed mathematical treatment followed shortly afterwards (12).

Sachse himself died in 1893 hardly 31 years old, a relatively unknown assistant at the famous Charlottenburg Institute (13). With these papers Sachse disappears from the pages of chemical history, and so, we are often told, do his *avant garde* proposals for the cyclohexane ring - at least for many years. How literally true that is we shall see, but certainly it was not until 1915 that the first determined attempt was made to rescue Sachse's theory from its undeserved oblivion. The author of this enterprise was Ernst Wilhelm Max Mohr (1873-1926), Professor of Chemistry at Heidelberg (14).

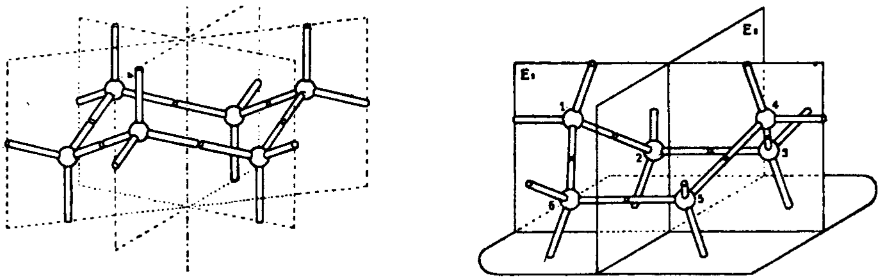
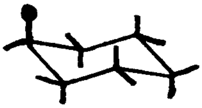
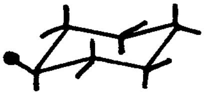


Figure 2. Mohr models for cyclohexane

In several papers over the next few years (15), Mohr elaborated on the Sachse concept of strainless, 6-membered rings, but made his point more clearly with illustrations of ball-and-stick models (rather than solid tetrahedra). But he also went further in another respect. Sachse had recognised the possibility of interconversion between forms, being especially easy in the varieties of "boat" conformations. In the absence of strong heat chair-chair interconversion would be less likely, so two varieties of "normal" monosubstituted cyclo-hexanes should exist:





One of the major objections to his theory had been that unambiguous proof for this was not forthcoming. Mohr, however, asserted that ring-inversion of chair-forms should be expected at ordinary temperatures through the impact of molecular collisions. Had this been all, the theory would have been rendered finally sterile as no empirical evidence could ever be expected to verify it. But it was saved from this ultimate humiliation by Mohr's recognition that ring-flip could not occur in one kind of situation: where the ring was locked into a larger molecule by some kind of ring-fusion. This, he asserted, would be the case with diamond, whose three-dimensional structure had been recently elucidated by Bragg (16).

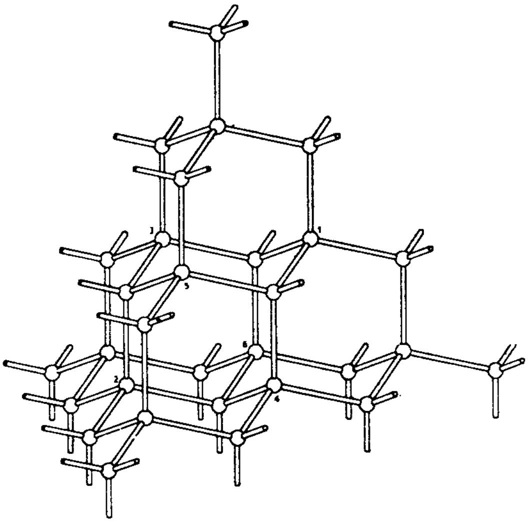


Figure 3. Mohr model for diamond

In fact the chair could be deduced from Bragg's X-ray diagrams. More simple than diamond, decahydronaphthalene should exist in 2 forms and these could not be interconvertible (unless a chemical bond was actually ruptured in the process).

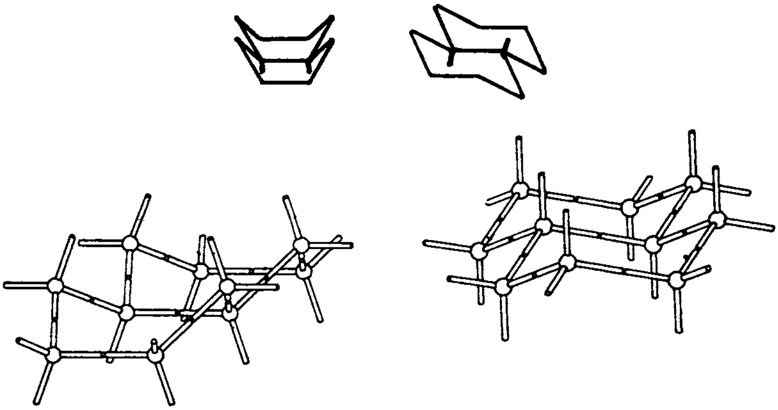
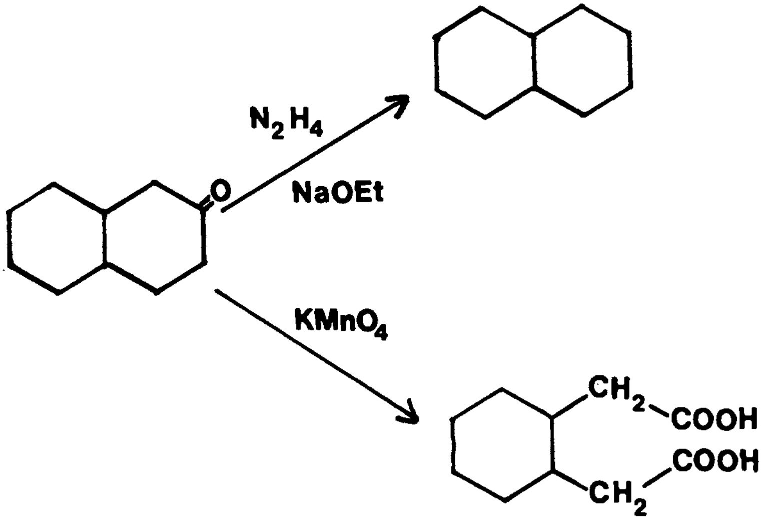
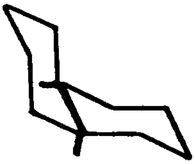


Figure 4. Mohr models for cis- *and* trans-*decalin*

Here was a further challenge to look for experimental evidence for a stereochemical hypothesis. It was accepted by W. Hückel who, in 1925, reported that decalin could be separated by fractional distillation into two isomers (17). By their relation to oxidation products they were termed *cis*- and *trans*- and allocated the 2 formulae above.



The impact of this work we shall discuss later. It is sufficient to note that Hückel's interpretation of his own work was not, in the end, correct. The first suspicions were voiced in 1943 by Odd Hassel (18). Realising the stereochemically unfavourable H-H interactions inherent in a single boat form (as opposed to a chair), he concluded that a 2-boat structure (for *cis*-decalin) was even more improbable, having no less than 5 eclipsed pairs and 2 flagpole-flagpole interactions. It was pointed out that a *cis* ring fusion could also be accomplished by means of two chairs:



Three years later he was able to establish this by electron diffraction (19) and other evidence confirmed it (20). But, back in 1943, he drew attention - almost for the first time - to an even more fundamental feature of the cyclohexane ring: the distinction between what we should call (21) axial and equatorial bonds but which he designated ϵ and κ. He emphasised the readiness with which ring-inversion converted a κ-substituent into an ϵ one and *vice versa*, and he made the profoundly important point that, generally speaking, monoderivatives have their lowest energy when the substituent occupies an equatorial position.

Seven years later Barton produced his paper in *Experientia* (3).

2. A Forgotten Hypothesis?

In this preliminary account I have simply recorded the principal milestones; or, to change the metaphor, the major peaks, ignoring altogether the fine structure of the early history of non-planar rings. One is often given the impression that Sachse and Mohr were very largely voices crying in a wilderness, prophets before their time, progenitors of a still-born hypothesis. Even Hückel, and to a less extent Hassel, do not significantly contradict that view.

Now if this is so we have a major problem on our hands. How could concepts of such immense value have failed to make their impact? Sixty years from Sachse to Barton, broken roughly halfway with Mohr's contribution, is a long time for hypotheses to lie dormant, even though the history of science has several parallel cases to offer. But the prior question, of course, is whether the impact of Sachse and Mohr *was* as minimal as that. Was it true, as is commonly said, that

Sachse's "theory was completely disregarded until 1918"? We must first establish that this was not the case.

Even a cursory glance through the literature reveals that Sachse's work was far from unknown. He had published in two well-known journals (7,11) and abstracts had appeared in English (22). In 1894 Bischoff's textbook on stereochemistry (23) acknowledged the merit of Sachse's concept of dynamic isomerism as applied to cyclohexane. At about the same time Arnold Eiloart was informing his audience at Cornell (24) of Sachse's suggestion of "another space-formula for hexamethylene" to account for the easy conversion of *cis*-dicarboxylic acids to *trans*.

There had been some early adverse reactions on rather general grounds. Hermann, in 1890, opposed the uses of tetrahedra in constructing models of 6-membered rings (25). A few years later Lachman commented on Sachse's theory that, "while geometrically excellent, it is incompatible with our views of valence, and may therefore lead to interesting developments of our valence conceptions" (26). It belonged more to the future than the present - a particularly shrewd comment, one may think.

Specific objections were also raised. An important contribution here was a paper (27) by Werner and Conrad in 1899 - just about the time that Werner was renouncing organic research for good. After referring to, and illustrating, the two strainless arrangements for cyclohexane proposed by Sachse they wrote:

> "These advantages of the steric formulae must be weighed against this disadvantage: they allow one to predict definite isomers for mono- and di-substitution products for which there has been so far no factual confirmation".

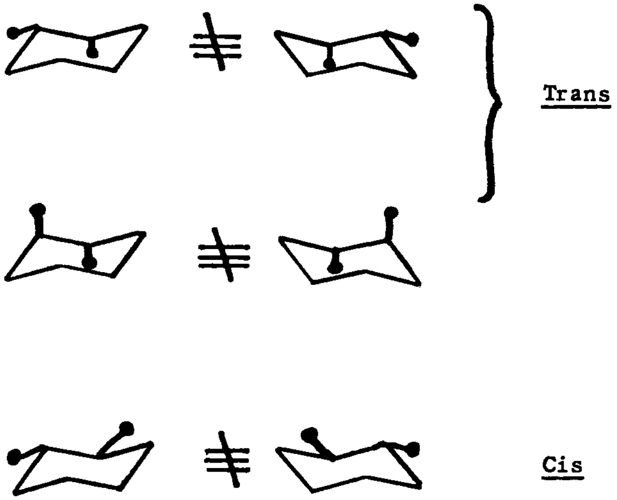
The existence of several mono-substituted cyclohexanes was a consequence of buckled ring structure. Taking only the relatively rigid "normal" form of Sachse, one would expect to find two isomeric forms, but these had not been unequivocally shown to exist in any one case, - though it does not seem that many intensive searches were originated. At one stage it had looked as though an example would appear. Sachse, in his 1892 paper, referred to the apparent existence of two acids $C_6H_{11}.COOH$, one from Caucasian naphthenic acids and the other from hydrogenation of benzoic acid. This had been the work (28) of the Finnish chemist O. Aschan (29) who had worked in 1890-1 under both Wislicenus and Baeyer. However Aschan's work was criticized by Markovnikov (who claimed exclusive rights to research on Baku petroleum acids and warned Aschan off) (30). The result was therefore inconclusive, with severe doubts remaining about the purity (and therefore the identity) of the products. Moreover, though Sachse invoked Aschan's name in support of his view, the Finnish chemist did not return the compliment and claim theoretical justification for his results. All that could be said with much certainty was that, so far, Sachse's hypothesis was an open question.

This certainly is the impression one gains from Hantzsch's *Elements of Stereochemistry* (1901). We are told that:

> "According to this hypothesis which is due to Sachse, the symmetrical configuration would indicate two mono-substituted stereoisomers, and as a matter of fact, two hexahydroxybenzoic acids are known, one obtained by the reduction of benzoic acid, the other being the hexanaphthalenecarboxylic (*sic*) acid". (*31*)

Yet despite this the subsequent treatment of the geometrical isomerism of cyclic compounds is entirely in terms of planar rings!

To return to Werner and Conrad, they proposed an alternative approach. Again making the minimum assumption of "chair" forms, they observed that "hexahydrophthalic acid" should exist as a resolvable *trans*-form and a non-resolvable *cis*-form. They came to this conclusion from models which were not described but were presumably like this:



Both cis and trans isomers should be resolvable, and this was attempted using fractional crystallisation of quinine salts. They concluded:

> "Despite numerous attempts there has been no success in separating from the cis form an active modification, whereas it is quite easy to resolve trans-hexahydrophthalic acid into its optical antipodes. If the negative result of our attempted resolution of the cis acid can be utilized for one valid deduction with regard to the question under debate, that result (taken in conjunction with the positive result for the trans acid) is that the assumption of a stable, steric arrangement of the carbon atoms in cyclohexane is not very probable" (32).

What is challenged, therefore, is not the shape but the stability of the strainless rings. As time went on the monosubstituted isomers became less credible than ever. In 1905 Aschan himself admitted "the non-existence of two forms of hexahydrobenzoic acid already weakens Sachse's idea" (33).

This was in his great textbook of alicyclic chemistry for which he received the Valbruch Prize - a bienniel award for the best scientific work in German (29). Its influence was considerable and helped materially to shape opinion on the Sachse hypothesis. He went on:

> "The fact that this view of the configuration of the hexamethylenes is not verified is probably to be explained on the grounds that Sachse's formulae represent only different phases of the movement within the molecules of the hexamethylene" (34).

In other words, for practical purposes, Sachse's strainless rings had little relevance. In 1907 Pattison Muir called them "an interesting chemico-geometrical development of the fundamental hypothesis of stereochemistry, especially to benzene and its derivatives" (35). Eight years later Beesley, Ingold and Thorpe wrote significantly that:

> "It is, of course, assumed there is no distortion of the angle of the hexagon caused by the attachment of groups to any one carbon atom of the cyclohexane ring" (36).

There was no question of any other value than 120° for each ring angle, - "of course"! Thorpe himself, who admittedly had his own axe to grind, wrote later that by 1915 it was almost universally held that the cyclohexane ring was planar (37).

So, in summary, it seems that though Sachse was not entirely forgotten his work was largely ignored. Ring-flip might or might not occur; even if it did, the net result was a planar average.

After Mohr's entry on the stage things could never by quite the same again. As we have seen, he exposed the implications of ring-inversion more thoroughly than any before him, proposed a specific test for his theory and related it all to the data and insights of physical chemistry. Yet for all that, conformational analysis had another 30 years of gestation.

Now, however, there appeared to be greater confidence in the reality of those chairs and boats. Occasionally they might be discovered as unwillingly rigid prisoners in a fused-ring molecule. Usually, however, they were transient entities of little concern to the working chemist. In 1919 Stewart could accept Sachse only "under the condition that his two configurations are vibration phases of the hexamethylene molecule" (38). Interestingly enough, he was saying the same thing nearly 30 years later: cyclohexane was "a labile system" (39).

In 1929 Haworth introduced the term "conformation" and applied it to models of glucopyranose and other monosaccharides. A diligent reader of Sachse (40), he had however to conclude that "at present there is insufficient experimental evidence available for any kind of opinion" on strainless rings in polysaccharides (41). He referred to the X-ray work of Spronsler and Dore on cellulose (42), composed of glucopyranose units thus:

Even this was not decisive enough for some. Haworth himself observed that if the decalin molecules could "be regarded as being built up by the fusion of two uniplanar cyclohexane rings, then, whereas the resulting cis-form is free from abnormal strain, the corresponding trans-form is seen to be considerably (though perhaps not unbelievably) strained" (43). That was the kind of price to be paid for a planar cyclohexane molecule.

It was also in the 1920s that Hückel separated the two decalins (17). At about the same time the work of Boëseken and the Delft school began on the boric acid complexes formed by condensation between acetone and cyclic 1,2-diols. (44).

Here the researches of Derx were specially noteworthy (45). He showed that cyclohexane-1,2-diol reacted with acetone only in the cis form, and illustrated his arguments with models of the type used by Mohr (though in his earlier work he was unaware of Mohr's papers). Yet his valuable insights were largely lost to view in the next 25 years - a further token of the enormous difficulty associated with the concept of three-dimensional strainless rings. Even more astonishing was a paper by Hendricks and Bilicke concluding, on the basis of X-ray data, that "β-benzene hexabromide" had a molecular symmetry consistent with a puckered cyclohexane ring, but asserting

> "Mohr's theory of 'Strainless Rings' as applied to cyclohexane and its derivatives is not compatible with our conclusions in so far as the solid state is concerned. His three-dimensional formulae... have a center of symmetry in one case, but not a plane of symmetry" (46).

This is so at variance with the facts that one can only assume that Mohr's proposal was totally misunderstood. Two years later Bilicke, with R.G. Dickinson (47), gave a clear diagram of the chair-form and specified a tetrahedral ring angle but gave no acknowledgment that Mohr could be right.

In general there is no doubt that most organic chemists would have agreed with these words of Thorpe in 1931 (48).

> "The multiplanar character of the rings beyond those containing six carbon atoms is now fairly generally accepted, as is also the uniplanar character of rings below those containing six carbon atoms. But the six-membered ring has still to rid itself of or adopt the Sachse-Mohr "arm-chair" or "boat" hypothesis.... At present there is no evidence either chemical or physical which supports the Sachse-Mohr hypothesis".

3. Obstacles to Progress

These words bring into sharp focus a major historical problem. Why did conformational analysis take so long to emerge after the original suggestion in 1890? This phenomenon of an apparently stillborn hypothesis is by no means unique in chemistry. Even more famous is the adoption of Avogadro's hypothesis, enunciated in 1811 but not generally used until the 1860's. In fact there is a remarkable parallel between the two cases. The remainder of this paper, inevitably more speculative than the first part, will attempt to identify some of the factors at work in the case of the Sachse-Mohr hypothesis.

3.1 Experimental Ambiguity.

It is, of course, extremely obvious that one great difficulty was that of formulating clear and unambiguous experimental tests for Sachse's multiplanar rings. As with Avogadro's hypothesis what were deemed to be simple tests for the theory proved later to be concerned with a whole complex of variables, not just one. This has been termed the Duhemian pitfall (49) after the philosopher of science who drew attention to it (50). Thus the identity or non-identity of all samples of the hexahydrobenzoic acid depends not only upon what we should call axial or equatorial substitution but whether or not interconversion by ring-flip could easily occur. Similarly, the non-resolvability of *cis*- hexahydrophthalic acid (27) tested not only its ring shape but also the optical stability of such a system. Where the case for rejection of a hypothesis rests upon purely negative evidence, as here, history should warn us to be careful.

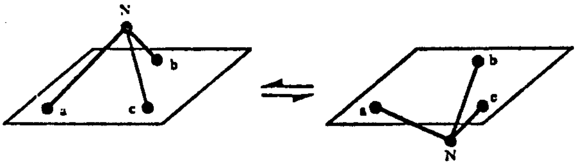
This was the point perceived so clearly by Mohr, and after his papers the nature of the historical problem slightly altered. But, for the first 25 or 30 years, the Sachse theory was very much a victim of the tests devised to prove it. Its reception was made even harder by the strength of the older alternative, associated with the name of Baeyer. Assuming planar rings he had predicted that the most stable members would be those with 5 or 6 carbon atoms. The discovery of a stable cyclopentane-1,2-dicarboxylic acid (51) shortly afterwards lent strong support to the theory while, in 1892, heats of combustion for tri-, tetra-, penta- and hexamethylenes again pointed to greatest stability in the last two members (52). Later on, numerous ring-contractions from 6 to 5 members were cited as further evidence, for a cyclopentane should be marginally less strained than a planar cyclohexane (53). The fact that ring-expansion could also occur but did not seriously prejudice the Baeyer theory's popularity emphasises perhaps that one sees what one is looking for.

However, as we have seen, after Mohr's papers the issues were clarified. The concept of a strainless 6-membered saturated ring then became obfuscated not by difficulties in testing but by sheer lack of interest. Its second phase was marked by the problem of relevance.

3.2 Relevance Factors. There seems no inherent reason why substantial progress could not have been made if chemists had been concerned to pursue the matter. On the whole they were not, and the problem of another 30 years' neglect resolves itself into a cluster of inter-related factors which I shall try to identify.

First there was the factor of *scientific theory.* How did the Sachse-Mohr hypothesis mesh in with the generally accepted theoretical framework of organic chemistry? The answer is a curious one. It seems impossible to separate the fate of cyclohexane from that of benzene. In the closing years of the last century theoretical organic chemistry was dominated by the unresolved problem of the benzene formula. One elegant solution had been the prismane structure of Ladenburg (54) but this had never gained much favour because, it was suggested (55), chemists treated such excursions into three dimensions with "extreme distrust". Its wedge-shaped shadow must have excluded a good deal of light from Sachse's 3-dimensional ring. But the alternative Kekulé structure led to the prediction of two ortho-disubstituted isomers and these, like the hexahydrobenzoic acids, had never been found. One was therefore forced to concede some kind of "oscillation" for benzene; but by so multiplying hypotheses one tended to bring an air of unreality to the whole argument. That is why, in the last three decades of the 19th century, chemical periodicals are littered with benzene formulae that attempted in various unconventional ways to express what was, in classical terms at least, inexpressible. At the turn of the century the dominant influence was not Kekulé but Thiele with his residual affinities (56).

With this background it is scarcely surprising that chemists were reluctant to lose their planar rings or to associate themselves too closely with hypotheses about "oscillation". In conformity with this last point it may be observed that another area of stereochemistry suffered in exactly the same way. This concerns the non-resolvability of amines of the type Nabc. They were regarded as being planar (57) until theoretical considerations were reinforced by other experimental data. It has been claimed that in the 1920s Meisenheimer first proposed that oscillation of the nitrogen atom was responsible.

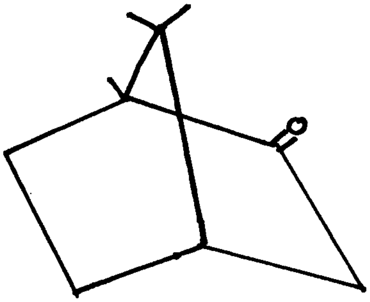


Yet an identical view was proposed by Walter for phosphorus and nitrogen and recorded in Berichte in 1873 (58). This was another unnoticed hypothesis; we do not even know the author's initials!

If the experience of benzene helped to discourage interest in Sachse's hypothesis, the effect would be magnified by a general reluctance to theorise on the fine structure of organic compounds. In Germany the great commitment was to synthesis, and organic chemistry was becoming top-heavy with accumulated facts. During the last half of the century about 100,000 new compounds were synthesised, of which "the majority were stillborn and their epitaphs are inscribed in Beilstein's Handbook" (59). Partly this arose from demands from industry - dyestuffs at first, then pharmaceuticals and explosives. It was also a result of the German Ph.D. system where "every Ph.D. in organic chemistry represents so many new compounds" (60).

To chemists preoccupied with these practical issues the speculations of Sachse must have had little apparent relevance. On the other hand those chemists at the turn of the century with a taste for theory were more likely to find satisfaction elsewhere than in the organic branch.

As the 20th century advanced various events within organic chemistry helped to turn the tide of opinion a little more in Sachse's favour. We can only touch on some of these. Around 1900 the worldwide challenge of camphor was at its peak and the recognition of its tricyclic structure:



made credible the concept of buckled rings. But in camphor they were kept rigid. The concept of mobile systems was also emerging as one of general importance (61). As Thorpe and Ingold observed in 1922 they "are special only in so far as the phenomenon which they exemplify is related to experimental and human limitations. Magnitudes which cannot be measured are no less important philosophically than those that can" (62). Then, again, the collapse of Baeyer's strain theory with its planar rings was inadvertently engineered by the syntheses of fairly stable large ring compounds by Ruzicka and Stoll. The latter remarked that Ruzicka complained to him:

> "Now we are faced with a terrible difficulty. A long time ago, Adolf von Baeyer demonstrated that rings of carbon atoms in excess of six in number are difficult of formation and that the difficulty increases with an increase in the number of carbons. And here we have a ring with 17 carbon atoms. How shall we ever succeed in synthesizing it?" (63).

This work began in 1926, after a 20 year gap.

Perhaps the most important moves towards general recognition of multiplanar rings came in the new 20th century emphasis on natural products. Interest in camphor and the terpenes and alkaloids branched out into steroids and natural macromolecules (cellulose, proteins etc.). The widespread occurrence of saturated rings in nature led to a gradual awakening of interest in their shapes and reactivities. As Barton has remarked of the obscurity of much of Böeseken's work: "I think myself that a theoretical treatment becomes well accepted only if there is a real need for a large body of chemists to use it" (64). The same consideration must apply to the Sachse-Mohr hypothesis itself. Gradually, over 60 years, the critical number of interested chemists (whatever that was) was being approached; by 1950 it had certainly been reached.

But we must look beyond the confines of organic chemistry itself, and that brings us to a factor of scientific organisation. It is obvious that the organic chemist does not usually employ concepts from astronomy or psychology, though he does draw upon results from physical chemistry. But that is true today, and 50 years ago was far from general. At that time the demarcation between the two areas was fairly strong. The position is well summed up by the characterisation of Thorpe's attitude to physical methods as one of "genial tolerance" and nothing more (65). It is said that W.H. Perkin Jr. held the view that "physical chemistry is all very well but it does not apply to organic substances" (66).

Nor was this approach to physical measurements a transient feature of pre-World War II organic chemistry. It deeply affected stereochemical thinking even after that. Here is Barton's analysis:

> "On the whole organic chemists in the 1940s did not pay much attention to stereochemistry. They knew of course how many stereoisomers there should be when they carried out a reaction, but they had very little idea of why you would get more of one isomer than of the other when you carried out an asymmetric synthesis. Stereochemistry was not treated with the attention it should have received and in particular nobody bothered very much about the shapes of molecules" (67).

Thus right through the first half of the present century the Sachse-Mohr hypothesis suffered from the neglect of physical data. Since it was only through physical data that the theory was to be fully validated, this attitude would clearly be unhelpful. But physical chemistry did not give only validation - it also offered relevance to the new doctrines of stereochemistry. Most of the early physical work was not done to prove the Sachse structures, but it gave the needed evidence as by-products of other work. So the buckled ring entered the consciousness of increasing numbers of chemists and became a live issue at last when someone was able to unite the two fields of knowledge.

In the 1930s diffraction by X-rays and by electron-beams was to be followed in the next decade by infra-red and Raman spectroscopy which, though controversial at first, led to fairly firm conclusions about chair and boat forms of cyclohexane (68). Another factor of importance was the application of thermodynamics to organic chemistry. This owed much to A. Michael who vigorously opposed Baeyer's strain theory as being too mechanical and deficient in the attention paid to energy relationships (69). Since then the thermodynamic approach has had much to offer to the study of molecular conformation.

In conjunction with spectroscopic data it led to a major advance in the 1930s: the recognition of hindered rotation about the carbon-carbon bond in ethane. Perhaps the most interesting case is afforded by the experience of Hassel whose interest in cyclohexane stereochemistry dates back to the 1930s. It was he who introduced into Norway the techniques of dipole moment measurement and electron diffraction. By 1943 he had enough data to lead to a general conclusion (18). Shortly afterwards he was arrested by the Nazis and not able to resume his electron diffraction work until after the war. In 1946 he was able to announce experimental vindication of his thesis that the chair-form was the preferred shape for cyclohexane (19).

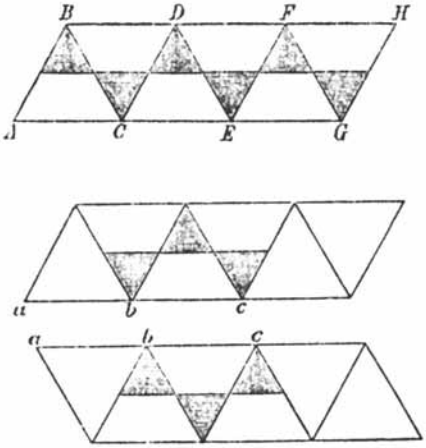


Figure 5. Sachse models of cyclohexane: construction diagrams

Top: Chair *Bottom: Boat*

Finally we can identify a relevant factor of scientific communication. The more easily ideas are communicated the more readily their relevance is seen. In the case of stereochemistry in general the role of models has always been important (70). My contention is that this was particularly true for the reception of the Sachse-Mohr doctrines. Sachse himself was aware of this and gave instructions for making strainless rings from cardboard tetrahedra (7). For long they dominated the stereochemical scene appearing as the frontispiece to the 6th edition of Stewart's Recent Advances in Organic Chemistry, vol. I (1931). The same author included directions for their construction in both editions of his Stereochemistry, observing "the subject is made much more comprehensible if models be used instead of plane formulae or perspective drawings" (71).

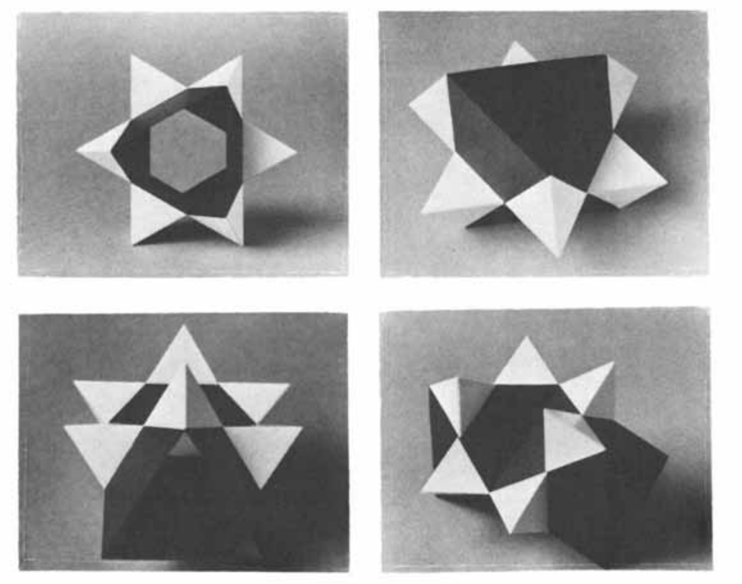


Figure 6. Sachse models of cyclohexane: the completed models

Valuable as these models were they lacked the clarity of tetrahedral ball-and-stick varieties, and,in the long run, they may have helped to obscure the conformational relations that they should have illustrated. Above all they failed to demonstrate rotational effects. It is therefore not without significance that Mohr gave illustrations of a different kind of model, apparently similar to the Dreiding models of today. Shortly afterwards a paper from Leeds by W.A. Wightman (72) reported a similar type of model, constructed for the study of rotations about single bonds. Strangely, he preferred the boat to the chair form for cyclohexane because of its greater response to molecular collisions.

Certainly it would appear no accident that the second phase of rather limited acceptance coincided with the use of greatly improved models. In 1918 Stewart gave his opinion that "if electronic models could be constructed their appearance would stimulate the chemical imagination much more rapidly than any mere written efforts can do" (73). If that was to be true of the electronic theory of organic chemistry it would even be more likely for the concepts of Sachse and Mohr.

As the use of models developed communication was further aided by the adoption of uniformly accepted terminology and by the employment of clearer diagrams in print.

Clear and accurate typography was a problem in the early 1950s as can be seen from the distorted diagrams often encountered. But in time acceptable representations replaced typographical monstrosities with exaggerated shapes and axial bonds emerging at right angles to carbon-carbon bonds. Again, it has been pointed out (6) that Hassel's important work from 1938 until the end of the war was relatively unknown because it has appeared in Norwegian in fairly obscure journals. Like Berzelius over 100 years before another distinguished Scandinavian chemist was the victim of a communications breakdown.

So in these ways the basic ideas advanced as far back as 1890 became slowly seen to be not merely correct but also relevant. As Stewart once wrote:

> "For want of just one connecting link, or even the addition of a few words to a statement which contains the key to a problem, the question may go unanswered for years"(74).

Eventually that connecting link was forged from an alloy of organic chemistry, physical chemistry and chemical physics. The outcome was the paper by D.H.R. Barton in 1950.

Acknowledgment

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13

From Configurational Notation of Stereoisomers to the Conceptual Basis of Stereochemistry

V. PRELOG

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This Symposium commemorates the appearance of two papers that were published a hundred years ago and constitute the foundation of "chemistry in space".

In the fall of 1874 van't Hoff (1) published in Dutch his 14-page pamphlet dated Utrecht, September 5th,1874. The paper by Le Bel (2) appeared in the issue of the Bulletin de la Société chimique de France dated November 5th, 1874, i. e. virtually simultaneously with van't Hoff's publication.

The two young scientists - van't Hoff was 22 and Le Bel 27 - were dealing with the problem of so called "excess isomers" (3). By considering which of these isomers are optically active and which not, they arrived at the conclusion that the ligand atoms on carbon form a stable tetrahedron - a conclusion which they bravely converted into a general postulate. On the basis of this postulate, and the ancillary assumption that there is, in essence, free rotation about single bonds, they were able to account for the number of the "excess isomers" - named later by Victor Meyer stereoisomers - and for their behaviour towards polarized light.

These novel and far-reaching ideas played a great role in the thinking of chemists who were concerned with natural products such as sugars, terpenes and alkaloids; and in this connection Emil Fischer's (4) utilization of the stereochemistry - as the "chemistry in space" was named by Victor Meyer (5) - was especially important. Fischer's unambiguous methods of determining the configuration of sugars by using symmetry arguments not only enabled him to rationalize the puzzling multiplicity of isomeric sugars but also substantially broadened the rather narrow experimental basis on which stereochemistry initially rested.

In van't Hoff-Le Bel Centennial; Ramsay, O.;
ACS Symposium Series; American Chemical Society: Washington, DC, 1975.

Apart from the intrinsic merits of Fischer's contributions the strong personality of this great experimentalist gave the stereochemistry a characteristic pragmatic stamp. It was very important for the quick spread and success of stereochemistry that already in his second paper "La chimie dans l'espace" (6) published in 1875, van't Hoff introduced the regular tetrahedron as a geometrical model for a carbon atom by means of which models isomorphous with molecules could be constructed. This enabled chemists to solve the problems which they encountered in their work by exhaustively inspecting the models. They did so for several decades without worrying about the geometrical basis of stereoisomerism or about the scope and limits of stereochemistry.

That is nicely illustrated by the following paragraph from Fischer's autobiography (7). He writes: "I remember especially a stereochemical problem. During the winter 1890-91 I was busy with the elucidation of the configuration of sugars but I was not successful. Next spring in Bordighera[where Fischer was accompanied by Adolf von Baeyer] I had an idea that I might solve the problem by establishing the relation of pentoses to trihydroxyglutaric acids. However, I was not able to find out how many of these acids are possible; so I asked Baeyer. He attacked such problems with great zeal and immediately constructed carbon atom models from bread crumbs and toothpicks. After many trials he gave up because the problem was seemingly too hard for him. Only later in Würzburg by long and careful inspection of good models did I succeed in finding the final solution".

Emil Fischer recognized that by using chemical transformations it is not only possible to correlate the relative configuration of several asymmetric carbon atoms in one molecule but that one can also often correlate the configurations of asymmetric carbons in different molecules. On the other hand, he was well aware of the fact that it is not possible to correlate by chemical methods the enantiomeric submicroscopic molecules with the macroscopic enantiomorphous geometrical models. To be able to use these models in his work he attributed one of the two possible models arbitrarily to one enantiomer of a compound which should act as reference compound and which he specified by the sign of its optical rotation with the calculated risk that this so-called Fischer convention had 50 percent probability of being wrong.

In the sugar series he first chose dextrorotatory glucose as reference standard. On that basis he tried to classify all the enantiomeric compounds that he was able to correlate by chemical transformations with dextrorotatory glucose, independently of their optical rotations, as *d*- and their enantiomers as *l*-sugars. Because of their relationship with (+)-*d*-glucose, (-)-fructose and (-)-arabinose belong according to Fischer to the *d*-series of sugars.

Unfortunately the letters *d* and *l* (as well as *D* and *L*) had been widely used before to specify the sign of rotation and it was often not clear what they really mean in a particular case. This inconvenience was finally eliminated by using small capital letters D and L for configurational notation, a convention that was endorsed by international nomenclature committees and soon found general acceptance.

Paul Walden's discovery (8) in 1896-99 that a replacement reaction can take a stereochemically different course depending on the reaction conditions imposed severe limits on the use of chemical transformations for classification of enantiomers: these reactions can be used only in cases in which the bonds on the asymmetric atom in question are not involved in the reaction or in which the steric course is mechanistically well substantiated. Emil Fischer was fully aware of this limitation but he overlooked in his early work the fact that if more than one ligand is changed by chemical transformations in the course of the correlation the assignment of an enantiomer into the *d*- or *l*-series depends on the reaction path used.

In a classical and lucid paper M. A. Rosanoff (9) showed that division of enantiomers into two classes is only possible by using some formal conventions. His diagram (Fig. 1) in which he correlated sugars with (+)- and (-)-glyceraldehyde as standart compounds and showed that some of Emil Fischer's generic correlations were based on a faulty principle is an early important contribution by an American scientist to general stereochemistry. To avoid confusion Rosanoff proposed that after his reform the misleading descriptors *d*- and *l*- should be replaced by Greek letters δ- and λ- but his proposal was not accepted by the chemical community.

An example that even Rosanoff's paper did not remove all controversies was the case of the tartaric acids. It is well known that (+)-tartaric acid can be chemically correlated either to (+)- or to (-)-glyceraldehyde depending on the reaction path used. According to the Rosanoff diagram it belongs to the λ- or L-series but this was never accepted by Emil Fischer and his school; it is interesting to see the confusion which this schism caused in various widely used European and American

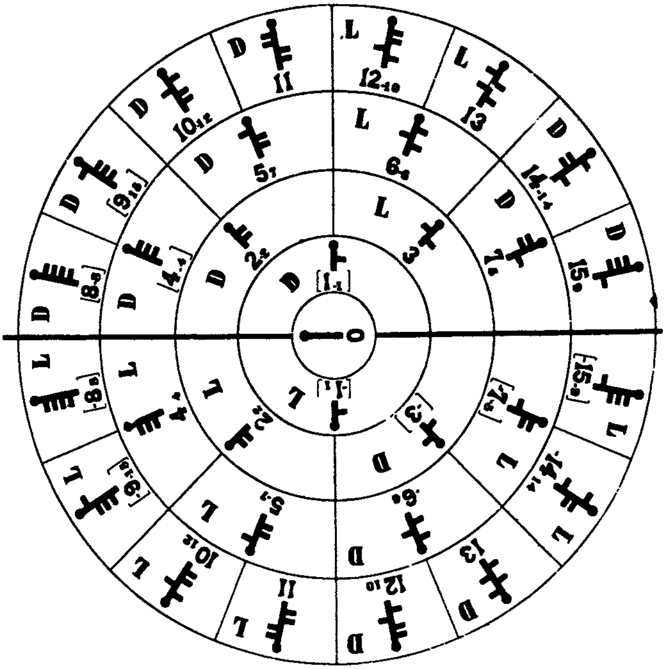

Figure 1

textbooks. It is therefore not astonishing that Karl Freudenberg wrote in his handbook of stereochemistry (1933) (10) "The prefixes d and l have a systematic meaning only in narrow limited groups: outside these groups no systematic meaning should be ascribed to them. The significance of such notations is very often overestimated".

In the period between 1930 and 1950 classifications of enantiomers analogous to those in sugar series have been proposed for several groups of compounds that could not be correlated to glyceraldehyde by chemical transformations. This made it necessary to choose several new standard compounds and conventions, and chemists working in the field often disagreed about them.

All this stimulated C. Buchanan to send a note to Nature (11) in which he wrote: "Although the relative configurations of many optically active compounds could be established, it is impossible to allocate the compounds to D- and L-series without ambiguity. This is true even in carbohydrate chemistry ...... Surely it would be better to abandon the used of prefixes D- and L, except for those parts of the carbohydrate and α-amino-acids fields in which they do serve a useful purpose".

This note appeared almost at the same time as an article by R. S. Cahn and C. K. Ingold (12) in which they laid down the principles of a configurational notation for tetrahedral asymmetric atoms which avoids the ambiguity of previous systems.

The most important part of the new system was the so-called sequence rule. The ligands around a tetrahedral atom were first ordered in a sequence by using atomic numbers (or in the case if isotopes atomic weights) as criterion. The constitutional differences among the ligands were established with the help of a directed hierarchical graph (Fig. 2) in sets which were equidistant from the central atom. The tetrahedral model with ordered ligands is then looked at from the side remote from the ligand of lowest priority (Fig. 3). A descriptor D was assigned to the enantiomer if the ligands starting with that of highest precedence are ordered clockwise, a descriptor L if they are ordered anticlockwise.

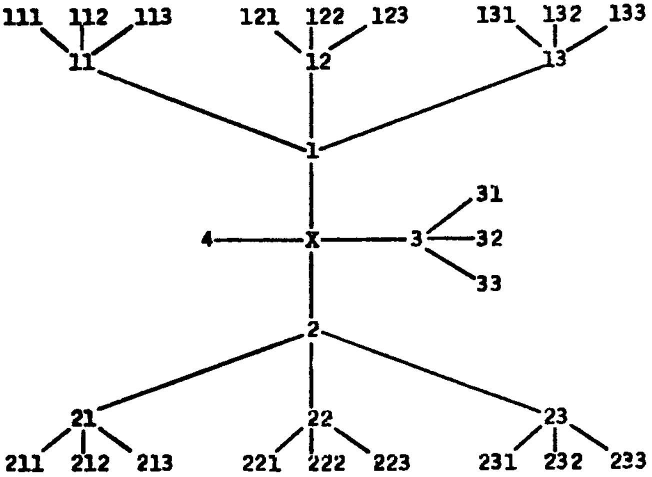

Figure 2

In 1954 the Anniversary Meeting of the Chemical Society was held in Manchester. It included a very successful

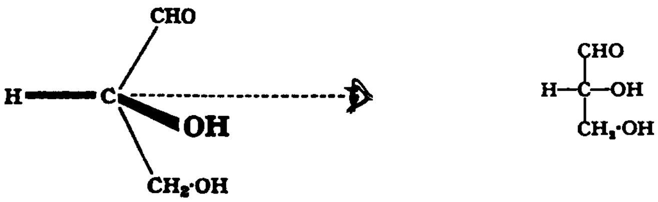

Figure 3

Symposium under the somewhat vague title "Dynamic Stereochemistry". At the end of the meeting, on April 2nd, a Reception and Dance were organized by ICI in its Hexagon House in Blakley. Among the few non-dancing participants the Editor of the Society's Journal, R. S. Cahn, the President of the Society, C. K. Ingold, and I tried to kill time drinking beer and talking chemistry. Among other things we discussed Cahn and Ingold's proposal for configurational notation. As the result of this conversation they invited me to join them in writing a paper about the Specification of Asymmetric Configuration in Organic Chemistry and I gratefully accepted their offer without the faintest notion of the consequences. We agreed easily by correspondence and during numerous meetings held in England and in Switzerland about the important principles which should guide us in construction of the system.

1. The new system should be general and absolute. General, to cover (or to be adaptable to cover!) all types of stereoisomerism. Absolute, because Bijvoet, Peerdeman and van Bommel (13) had by then confirmed by X-ray analysis that Emil Fischer's correlation of the chirality of molecules and models was correct; the arbitrariness of the choice was therefore eliminated.

2. The new system, like Cahn and Ingold's original system, should be based on a few exact rules which should be controlled only by the system itself and must not depend on nomenclature, numbering and/or other arbitrary factors beyond its control such as structural resemblance or genetic concepts. A one-to-one relation between a molecule and its stereochemical descriptor, i. e. that it must be impossible for the rules to lead to opposite descriptors for one enantiomer, is essential and the validity of the descriptor can be guaranteed only if this condition is fulfilled. The sequence rule of Cahn and Ingold was to remain the core of the new system but needed to be extended.

3. The new system should not be based on projection formulae. Additional rules would be necessary to account for the neglected dimension. Or as Ingold aptly formulated it: "Projection formulae are good slaves but bad masters".

4. To distinguish the new system from the previous ones new descriptors should be chosen. After consideration of many others, descriptors R and S (r and s) were selected for many obvious reasons.

As the result of our endeavour a paper appeared in 1956 in the Swiss journal Experientia (14) in which our ambitious program and proposals for the solution of various problems in connection with the specification of configuration were published. In addition to centers of asymmetry the concepts of axes and planes of asymmetry were introduced.

These proposals have been criticized from different sides. I shall not discuss here the criticisms of authors who did not accept the general principles, which we considered essential for the functioning of any such system. Of great value, however, were the comments of colleagues who accepted our proposals and used them in their daily work. The most important of such users were the Editors of Beilstein's Handbuch, the late Professor F. Richter and his colleague Dr. O. Weissbach. The latter undertook the Herculean task of specifying many thousands of stereoisomers of all types by our system. In addition he invented many ad hoc cases to test it. This labour, which we later named "Beilstein test", and the subsequent positive and benevolent criticism by Richter and Weissbach as well as by some other colleagues stimulated us not only to improve our system where necessary but also to extend it substantially. This was done rather slowly and with much deep thought and many fraternal arguments between 1961 and 1966. The resulting paper appeared in Angewandte Chemie (15). The original English text was translated into German (16) by Dr. H. H. Westen who, in the last stages, also made some essential corrections and conceptual contributions.

The "Beilstein test" persuaded us that we were on the right track; no other system was ever applied on such a large scale. The corrections and improvements we had to make in the third paper were substantial but the consequences were minor and the descriptors previously assigned to only a few compounds had to be changed. The most important extensions in it included the treatment of conformational stereoisomerism and of the helicity in general as well as the specification of chirality of octahedral complexes. We recognized that we were specifying by descriptors the "handedness" of molecules or of the parts thereof. It was very convenient to use for "handedness" the term "chirality" coined by Lord Kelvin (17) many years ago and rediscovered by theoretical physicists (18). We therefore gave our paper the title "Specification of Molecular Chirality".

During the last stages of writing we were aware that this would be our last common paper on the subject and we mentioned it sometimes in the course of our discussions. Sir Christopher managed to write the final version of the text in spite of his preoccupation with the manuscript of the 2nd edition of his monumental "Structure and Mechanism in Organic Chemistry" (19). He insisted that publication should not be delayed although during the reading of galley proofs we encountered some conceptual difficulties. Possibly he had a presentiment that he would have to leave us in not too distant future. I would like to confess here that the cooperation and contacts with this great man are among the most important events of my scientific life.

Through cooperation on the papers about conformational notation and the specification of molecular chirality I became aware, as already mentioned at the beginning of my talk, that stereochemistry developed as a pragmatic science and that its concepts were neither well defined nor appropriately taught. The geometrical fundamentals had not been separated from the physical consequences, as is in many instances evident from the terminology. In every textbook of organic chemistry old misnomers such as "geometrical isomers", "optical antipodes", "optical isomerism" etc. are still used for fundamental concepts. In fact all stereoisomers are geometrical isomers, and enantiomers are not "antipodes" (i. e. rotated by 180°!). Enantiomers are optically active but the enantiomerism itself is a geometrical feature; the optical activity is only a consequence of the symmetry, as are dipole moments of compounds without a center of symmetry. It is indeed possible to imagine a perfect stereochemistry without a knowledge of the phenomenon of optical activity. To determine the scope and limits of stereochemistry it is necessary to trace it to its geometrical source and that is chirality. Chirality in three-dimensional space is well known, but the less familiar two-dimensional chirality plays an equally important role (20),(21).

By combining equal and different two- and three-dimensionally achiral and chiral building blocks a catalogue of geometrical figures can be constructed which are isomorphous models for all types of stereoisomers. The items of such a catalogue are examples of classical and new stereochemical concepts such as elements of chirality, pseudoasymmetry, prochirality, heterotopy etc. It is beyond the scope of my lecture even to sketch how, in my opinion, that can be achieved. I have here wished only to illustrate how efforts to solve a seemingly simple problem, such as to fix conventions for configurational notation, can become a starting point for thoughts about the framework and structure of stereochemistry as a whole.

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