

## J. H. VAN'T HOFF AND J. A. LE BEL— THEIR HISTORICAL CONTEXT<sup>a</sup>

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To assemble and interpret for the first time a mass of knowledge, to see order where no order had been perceived before, represents one of the greatest intellectual achievements in science. The triumph of the organic chemists of the nineteenth century was just this. They established the structural theory of organic chemistry in the face of the enormous difficulties of uncertain atomic weights and uncertain molecular formulae, and even doubts about the real existence of atoms, until well into the second half of the nineteenth century. In this article we are specifically concerned with the achievements of van't Hoff and Le Bel in establishing a theory of organic stereochemistry. Before we can appreciate this pinnacle of nineteenth century chemical theory we must place it in the context of its time.

It is widely believed that before the theories of van't Hoff and Le Bel were put forward chemists did not think of molecules as three dimensional entities. This is certainly wrong. From the early part of the nineteenth century there was a duality of views about the reality of the structure of molecules and the use of chemical formulae. Some chemists held consistently to one or the other extreme viewpoint, others were torn between the two. The first school of thought, whose views by and large held sway up to the acceptance of the tetrahedral carbon atom, held that one could never obtain information about the physical structure of molecules, that molecules might have no physical structure, and that chemical formulae were merely useful adjuncts for systematising chemical reactions. On this viewpoint atoms and molecules were merely useful abstractions that could correlate chemical facts when manipulated according to certain rules, but whose reality was uncertain or even undeterminable. Chemists with this attitude

were quite naturally slow to attribute the spatial properties of real objects to atoms and molecules, particularly since such properties were not always reconcilable with existing physical theory. The tetrahedrally directed affinities in van't Hoff's model of the carbon atom were not acceptable to some chemists, particularly when used to explain the stereochemical features of double and triple bonds. At its best this sceptical tradition strongly influenced Le Bel who long remained open minded about non-tetrahedral arrangements for groups attached to saturated carbon atoms (even for CX<sub>4</sub> molecules). At its worst it must surely have played a part in Kolbe's famous and ill-judged diatribe<sup>1</sup> against van't Hoff and his great early supporter Wislicenus (*vide infra*), but *not* Le Bel, in which Kolbe writes of "... the most important problems in chemistry which may well never be solved—in particular the question of the spatial arrangement of atoms—...". The second school held that atoms and molecules do have a real physical structure in the obvious sense that we use today, even in the absence of direct confirmatory evidence. As early as 1808, immediately following the publication of Dalton's atomic theory, Wollaston<sup>2</sup> wrote of the need "... to acquire a geometrical conception of the atoms' relative arrangement in all three dimensions..." and he went on to speculate on the possible arrangements of atoms in molecules, including a regular tetrahedral arrangement of four atoms surrounding a fifth. Biot<sup>3</sup> and Pasteur<sup>4</sup>, before theories of molecular structure were possible, recognized that the optical activity of organic compounds in fluid phases implied that the constituent molecules must be dissymmetric and therefore three dimensional. It was this tradition of thought, acting on Kekulé's<sup>5</sup> and Couper's<sup>6</sup> discovery of the quadrivalence of carbon and accumulating experimental evidence about the structures of optically active compounds, that led to van't Hoff's<sup>7</sup> and Le Bel's<sup>8</sup> independent explanations of the structural origins of optical activity.

The dilemma posed by these opposing schools of

<sup>a</sup>This review is most closely concerned with events and ideas in the period just before and just after 1874. A less detailed review but with a much broader historical perspective may be found in "Models and Molecules" [(W. D. Ollis, *Proceedings of the Royal Institution*. 45, (1972)]

thought can be seen in the first volume of Kekulé's *Lehrbuch* (1861)<sup>9</sup> "Some chemists are still of the view that from a study of chemical metamorphoses one can derive the constitution\* of compounds with certainty and can express in a chemical formula this position of the atoms. That this last is not possible does not need special proof; it is self evident that one cannot show the position of atoms in space, even if one had investigated this, on the plane of the paper by putting letters together; for this one would need at least a perspective drawing or a model. But it is likewise clear that one cannot determine the position of atoms in a specific compound by a study of metamorphoses, because the way in which the atoms leave a changing and decomposing compound cannot indicate how they are arranged in the existing and unaltered compound. Certainly it must be considered a problem for research workers to discover the [structures] of the materials, and thus, if you will, the position of the atoms, but this can certainly not be accomplished by the study of chemical changes, but only by comparative studies of the physical properties of the unchanged compounds. It will then perhaps be possible to draw up [structural] formulae of chemical compounds which naturally must then remain the same for one and the same compound. But even when this is successful, the various rational formulae (transformation formulae) will always be needed because it is evident that with atoms arranged in a given way, a molecule will split in different ways and thus can give fragments of different size and different composition." In a sense Kekulé's position was unassailable but he had failed to recognise the implications of his own discovery. In fact organic chemists in the next 60 years correctly inferred the general nature of the structures of enormous numbers of organic compounds before any direct structural evidence became available from physical methods.

By the middle of the nineteenth century the fact of isomerism and the success of the concepts of radicals' and 'types' had established that molecules could not be characterised by composition alone and must therefore have structures, if atoms and molecules really existed, which many chemists doubted. Progress in elucidating structures, however, required three developments. The first was the establishment of the valency of carbon and thence a recognition of bonds between pairs of carbon atoms. Less obvious but almost equally necessary was a formalism for depicting constitutional formulae in an unambiguous manner for all possible organic molecules. The third was the realisation of the one to one correspondence be-

tween a structural formula and a molecule of a compound for most organic compounds.

In 1858 Kekulé<sup>5</sup> in Germany and Couper<sup>6</sup> in Scotland independently discovered the basic idea on which structural organic chemistry is based: that carbon is quadrivalent and its atoms can join with one another to form chains of carbon-carbon single, double, or triple bonds. This theory was particularly remarkable because it appeared when there was still uncertainty about atomic weights and molecular formulae. In 1860, for example, what was probably the first large international chemistry conference was held in Karlsruhe, attended by over one hundred leading chemists, with the intention of clearing up the controversy about atomic weights.<sup>10</sup> That this conference discussed, among other issues, "Is it convenient to make a distinction between the terms 'molecule' and 'atom'?" indicates the confusion and uncertainty common in chemistry at that time. Although Kekulé's paper was written using the symbolism of Gerhardt's theory of types while Couper's paper had only a very crude form of structural formulae (see Figs 1a and 1b) the way was clear for the appearance of constitutional formulae which would show whether pairs of atoms are bonded or not for all possible pairs of atoms in a molecule. Until constitutional formulae were fully developed it was not even possible to distinguish (constitutional) isomerism from stereoisomerism.

The establishment of the quadrivalence of carbon was not enough in itself. The need for a clear formalism for chemical structures is well illustrated by Kekulé's mistaken belief that three isomeric alcohols  $C_3H_7OH$  should be possible.<sup>11</sup> This mistake arose because Kekulé's "Lehrbuch" formulae (Fig 1b) were poor symbols for depicting the constitution of a molecule, even though they go far beyond the limitations of the theory of 'types' formulae (Fig 1a). Although Couper's formulae were from the first intended to be structural, the real breakthrough came with Crum Brown's graphical formulae (Fig 1d),<sup>12</sup> which were a startling advance on earlier formalisms and which have not been altered in a fundamental way even now. Crum Brown, however, explicitly denied that his formulae showed the (relative) physical positions of atoms in a molecule. The bonds, as we should now call them, were intended to show relative 'chemical' positions, i.e., the topological relationship, of the atoms only. Even more modern in some respects were Frankland's formulae (Fig 1e).<sup>13</sup>

In 1861 Butlerov<sup>14</sup> coined the term "chemical structure" and used it in the context of a one to one correspondence of structure to molecule, in the sense we understand today. During the 1860s it became common for some organic chemists to present formulae for molecules with a caveat that the formulae might, or might not, be valid models of the physical structure of the molecule. Others clung

\*We will use constitution, in our own text and in quotations, to mean the way in which atoms are joined together *without* stereochemical implications, and structure for all aspects of the organisation of atoms in molecules.



van't Hoff's approach and the elegance of Le Bel's argument contrast with and mark the end of the preceding series of long and complex polemical arguments. What both men had realised, although this was not stated as such in their papers, was that three dimensional molecules must have symmetry properties which should govern certain types of chemical and physical behaviour. More importantly both men were able to apply their realisation. Le Bel applied it to optical activity whilst van't Hoff applied it in a wider field. The doubt that Kekulé had expressed in his *Lehrbuch* (*vide supra*) that chemical transformations would ever supply the key to the three dimensional structure of molecules could now be dismissed for large parts of organic chemistry. Symmetry properties, such as the number of isomers possible for a given constitutional formula, were shown to be usable instead. This was a remarkable advance in chemical theory.

Van't Hoff, from Holland, and Le Bel, from Alsace, knew each other well, for they had been contemporaries in Wurtz's laboratory in Paris. Of this period van't Hoff later wrote "... That shortly before this we were working together in Wurtz's laboratory was purely fortuitous and we never exchanged a word about the tetrahedron there, though perhaps both of us already cherished the idea in secret."<sup>22</sup> Although the proposals put forward by Le Bel and van't Hoff are very similar the origins of their ideas were different. Le Bel was fascinated by the symmetry of polyhedra\* and developed his ideas from the works of Pasteur†: "... The works of Pasteur and many other distinguished workers have established beyond any doubt the correlation that exists between the dissymmetry of molecules and their optical rotatory power."<sup>8</sup> Van't Hoff, on the other hand, developed his ideas directly from those of Kekulé: "... If one accepts... that the four valencies of carbon are represented by four directions..."<sup>7b</sup>

Le Bel's paper is largely concerned with the relationship between molecular dissymmetry and optical rotation and only once does he mention the tetrahedral carbon atom. Van't Hoff takes a somewhat wider view. After giving strong evidence for the tetrahedral carbon atom in terms of the number of isomers likely if any other arrangement of valencies were present, he goes on to discuss (a) optical rotation, (b) the number of isomers possible with two asymmetric carbon atoms, (c) the representation of double bonds, from which he advances the first satisfactory explanation of the

isomerism of maleic and fumaric acids, and (d) the triple bond which he clearly regards as linear. Van't Hoff first published his ideas in Dutch,<sup>7a</sup> but so little notice was taken of them, as he might have expected, that he translated his paper into French,<sup>7b</sup> in which language it appeared within a few months of Le Bel's paper. It was several years, however, before chemists generally started to take note of the work. Landolt, for example, wrote a paper in 1876<sup>23</sup> on the optical rotatory power of camphor without mentioning the work of these two unknown young chemists. It was two years later still in another paper on optical rotation<sup>24</sup> that he acknowledged the work of Bel and van't Hoff, giving a clear indication that he accepted spatial arrangements of atoms as a part of molecular structure.

Real recognition began in November 1875 when Wislicenus asked van't Hoff for permission to publish a German translation of his paper by Dr. Herrmann. Wislicenus wrote to van't Hoff: "May I inform you that your theoretical development has given me much pleasure and great enjoyment, and in it I see not only an unusually ingenious attempt to explain facts that have hitherto not been cleared up, but also I believe that it will provide a goodly number of suggestions for our science and hence be of epoch-making significance." When the German translation<sup>7c</sup> was published in 1876 the way was open for the gradual acceptance of the theory‡

Unfortunately all was not sweetness and light thereafter. In 1877 Kolbe, one of the most distinguished and respected of the older German chemists felt impelled to launch a tirade<sup>1</sup> against van't Hoff and more particularly Wislicenus for accepting the theory. This famous attack is worth quoting in full.

#### *Signs of the Times*

by H. Kolbe

In a recently published paper with the same title, I pointed out that one of the causes of the present regression of chemical research in Germany is the lack of general, and at the same time thorough chemical knowledge; no small number of our professors of chemistry, with great harm to the science, are labouring under this lack. A consequence of this is the spread of the weed of the apparently scholarly and clever, but actually trivial and stupid, natural philosophy, which was displaced fifty years ago by exact science, but which is now brought forth again, out of the store room harbouring the errors of the human mind, by pseudoscientists who try to smuggle it, like a fashionably dressed and freshly rouged prostitute, into good society, where it does not belong.

Anyone to whom this concern seems exaggerated may read, if he is able to, the book of Messrs. van't Hoff and Herrmann on the *Arrangement of Atoms in Space*, which has recently appeared and which overflows with phantasies. I would ignore this book, as many others, if a reputable chemist had not taken it under his protection and warmly recommended it as an excellent accomplishment.

A Dr. J. H. van't Hoff, of the Veterinary School at Utrecht, has no liking, apparently, for exact chemical in-

\*He recommends his readers to study the theorems proposed by Bravais relating to the symmetry of polyhedra and crystallographic studies.

†In his "Leçons sur la dissymétrie moléculaire" Pasteur suggested a tetrahedral grouping of atoms.<sup>4</sup>

‡E.g., the Royal Society (London) waited until 1893 before awarding the Davy Medal to van't Hoff and Le Bel.

vestigation. He has considered it more comfortable to mount Pegasus (apparently borrowed from the Veterinary School) and to proclaim in his *La chimie dans l'espace* how the atoms appear to him to be arranged in space, when he is on the chemical Mt. Parnassus which he has reached by bold flight.

The prosaic chemical world had little liking for these hallucinations. Therefore Dr. F. Herrmann, Assistant at the Agricultural Institute at Heidelberg, undertook to give them wider vogue by means of a German edition. This carries the title "*The arrangement of Atoms in Space*, by Dr. J. H. van't Hoff; translated into German from the author's monograph *La chimie dans l'espace* by Dr. F. Herrmann, Assistant at the Agricultural Institute in Heidelberg; with a foreword by Dr. Johannes Wislicenus, Professor of Chemistry at the University of Würzburg. . ."

It is not possible to criticise this work even half thoroughly because the play of phantasy in it dispenses completely and entirely with any factual basis and is absolutely unintelligible to the sober scientist. To get an idea of what the authors had in mind it is enough to read the following two sentences. The paper begins with these words: "Modern chemical theory has two weak points. It says nothing about the relative positions of the atoms in the molecules, nor anything about their movements." The other sentence from page 35 says: "In the asymmetric carbon atom we have a medium which distinguishes itself by its helical arrangement." To counter the argument that one may not quote sentences out of context I refer to the paper itself. One will be convinced that these sentences are as unintelligible when in conjunction with the others as they are by themselves. As I have said, I would have taken no notice of that work if Wislicenus had not inconceivably written a foreword for it, and, not jokingly but in complete seriousness, warmly recommended it as a worthwhile contribution—whereby many young and inexperienced chemists might be misled into assigning some value to these shallow speculations. Wislicenus says the following in his foreword: "I have been compelled by my work on lactic acid to say that the facts force one to explain the differences between isomeric molecules of the same constitutional formula by different arrangements of their atoms in space, and to openly support the validity of taking geometrical concepts into the context of molecular structure."

It is a sign of the times that modern chemists feel themselves qualified and able to give an explanation for everything, and, when the results of experience are not

sufficient, they seize upon supernatural explanations. Such treatment of scientific questions, which is not far from belief in witches and from table-tapping, even Wislicenus considers to be admissible. He continues as follows: "The credit for having taken this step in this particular way is due to van't Hoff. The fundamental idea of his theory lies in the proof\* that compounds of a carbon atom with four different simple or compound radicals exist as two different isomers. This idea struck me as very remarkable when reading van't Hoff's paper *La chimie dans l'espace*, and I was absorbed by the further mathematical formulation and the practical applications to geometrical isomerism, which become more and more numerous, and to the optical activity of organic compounds. It may be that not all that van't Hoff says is essential for present requirements and that some of the special applications may not be completely confirmed in the future, but the theory of carbon containing compounds has taken a large step forward, and that this step is an organic and necessary one.† He [it]‡ develops the ideas that have been best founded up to now in a logical way and supports them by extending them to actually observed cases which seem to lie beyond their limits."§ Wislicenus makes it clear that he has left the ranks of exact scientists and has gone over to the camp of the natural philosophers of ominous memory, who are only by a narrow "medoium" separated from the spiritualists.

#### End of translation of *Signs of the Times*

Modern chemists find it difficult to comprehend such bitter and vituperative attacks by one chemist on another but Kolbe's paper was simply the last, and perhaps most ill-judged, great example of personal attacks in journals. Liebig and Kolbe in particular abused their positions as editors to mount attacks from very conservative positions on new ideas.<sup>25</sup> Whereas Liebig's attacks were often appallingly successful in harming the scientific standing on his victims, Kolbe's polemics tended to misfire and drew attention to ideas that might otherwise have been slow to spread. Kolbe himself should not be judged by his editorial lapses. According to H. E. Armstrong,<sup>26</sup> who had worked in Kolbe's laboratory, Kolbe was "... one of the most thorough and typical Germans of the old school it has been my good fortune to meet, a chemist who received scant justice from his own countrymen—few realised the extent to which he was the founder of our modern system of constitutional formulae—because he dared to criticise and expressed himself in the biting terms of a clear and concise diction, in a pure German which no one else in those days had at his command: in fact he took his countrymen to task for their slovenly language. . ." Talking of Kolbe as a teacher Armstrong says "... Whatever suggestion we made to Kolbe he never discouraged us; his habit was to grasp the lapels of his coat, then to reply: 'try it, try it'. We disputed with him constantly at the blackboard, nearly always taking exception to his theoretical views—but without his being offended. . ." Here then we have a picture of an older and scientifically very conservative man

\*Where on earth has this proof been given, and since when have games been called chemical theories.

†What does the theory of carbon containing compounds mean? What does it mean to say that this step is an organic and necessary one? Clarity of ideas and intelligibility of expression are going more and more out of fashion in modern chemistry.

‡Which? Van't Hoff or the step?

§[Kolbe quite rightly attacks both the grammar and the logic of this sentence which is as bad in German as in its English translation.] What does this sentence mean? "Actually observed cases which seem to lie beyond their own limits", or, if "their" refers to the best founded ideas, what does the sentence then mean, the actually observed cases which lie beyond the limits of the best founded ideas?

given to disputes, with much work in the field of the constitution of organic molecules, the significance of which was probably underrated by his contemporaries, whose theoretical views differed from those of his younger colleagues, and who possessed a biting command of the German language. Unfortunately he came to use his powers to abuse rather than to understand new ideas. In common with other attacks that have been made by the establishment on new and sound scientific theories (e.g. the inquisition attacking Galileo's advocacy of the Copernican theory) the attack was upon the man, the basis of the theory was not, and could not be attacked, because its opponents did not understand it.

Kolbe's attack probably drew attention to van't Hoff's work even more effectively than did Wislicenus' support and ensured that it did not remain in obscurity. This was valuable because van't Hoff soon turned his genius towards physical chemistry, for which he received the first Nobel Prize in Chemistry in 1901, and unlike Le Bel did little further work on organic stereochemistry. The working out of his ideas on the stereochemistry of olefines and allenes, and the obvious extension from chiral carbon atoms to other chiral centres, was left to other chemists. Perhaps this was fortunate because the experimental difficulties with allenes in particular prevented van't Hoff's prediction<sup>7c</sup> from being realised until 1935.<sup>27</sup> Surely one of the longest periods between prediction and experimental verification in modern science!

Van't Hoff's ideas about double bonds were particularly disliked by many chemists because they were not consistent with nineteenth century physics. Claus<sup>28</sup> and Lossen<sup>29</sup> criticised this aspect specifically, while von Helmholtz's despairing cry about organic chemistry in general, "The whole extraordinarily comprehensive system of organic chemistry has developed in the most irrational manner, always linked with sensory images which could not possibly be legitimate in the form in which they are presented"<sup>30</sup> must have applied most of all to daring speculations such as van't Hoff's tetrahedral carbon atom. Van't Hoff's ideas, however, developed fruitfully in many directions, e.g., the Baeyer strain theory, Sachse's and Mohr's work on the conformations of cyclohexane, Fischer's elucidation of the configuration of carbohydrates, the chirality of suitably substituted ammonium, phosphonium, and sulphonium compounds, before direct physical evidence for the shapes of molecules became available from X-ray diffraction.

Le Bel remained active in the field of stereochemistry for many years, devoting much of his effort to clearly delineating the differences between his ideas and van't Hoff's.<sup>31</sup> In 1890 Le Bel wrote "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<sub>4</sub> have the shape of a regular tetrahedron." He concluded from the crystal symmetries of solid CBr<sub>4</sub> and Cl<sub>4</sub> that the molecules could not be regularly tetrahedral. He attempted to resolve citraconic and mesaconic acids as well as compounds of the type CR<sub>2</sub>R'R" in order to falsify van't Hoff's tetrahedral carbon atom and, particularly, the model of a carbon-carbon double bond derived from it.

Le Bel also made studies of racemisations that might result from the flexibility of bonds that he felt must allow an asymmetric molecule to change into its enantiomer without breaking of bonds. Just as many of the consequences of van't Hoff's simple rigid tetrahedral carbon atom were only realised experimentally much later, so also the flexibility of valencies that Le Bel believed in were not found for many years until Meisenheimer suggested that amines of the type NRR'R" are pyramidal but can readily invert and therefore can not be resolved, and the spectroscopic detection of inversion in ammonia confirmed this. Even closer to Le Bel's ideas of flexible atoms are the thermal racemisation of tricoordinate sulphur compounds and the pseudorotation in phosphoranes.

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