CROATICA CHEMICA ACTA
CCACAA **79** (3) XLIX–LVII (2006)
© THE NOBEL FOUNDATION 1975

CHIRALITY IN CHEMISTRY

Nobel Lecture, December 12, 1975
by VLADIMIR PRELOG
ETH, Laboratory of Organic Chemistry, Zürich, Switzerland

An object is chiral if it cannot be brought into congruence with its mirror image by translation and rotation. Such objects are devoid of symmetry elements which include reflexion: mirror planes, inversion centers or improper rotational axes.

The useful terms chiral and chirality were coined by W. H. Thompson (Lord Kelvin) in 1884 and are derived from *cheir*, the Greek word for a hand, indeed one of the most familiar chiral objects. The simplest chiral object of the three-dimensional perceptual space is, however, the chiral three-dimensional simplex, the irregular tetrahedron. As early as 1827 the famous German mathematician August Ferdinand Mobius (of the Mobius-strip) pointed out that the volume of a tetrahedron, expressed as a determinant involving the Cartesian coordinates of its labelled vertices, and of its mirror image have different signs, which are not dependent on the position of the tetrahedra but change by reflection.

Many objects of our three-dimensional perceptual world are not only chiral but appear in Nature in two versions, related at least ideally, as a chiral object and its mirror image. Such objects are called enantiomorphous or simply enantiomorphs. There are enantiomorphous quartz crystals (Fig. 1), pine cones, snail shells, screws, shoes *etc*.

The genius who first suggested (on the basis of optical activity) that molecules can be chiral was around 1850 Louis Pasteur. He also showed by his famous experiments with tartaric acids that there is a connection between enantiomorphism of crystals and of molecules.

The Swiss painter Hans Erni has drawn for me the paraphernalia necessary for dealing with chirality (Fig. 2):

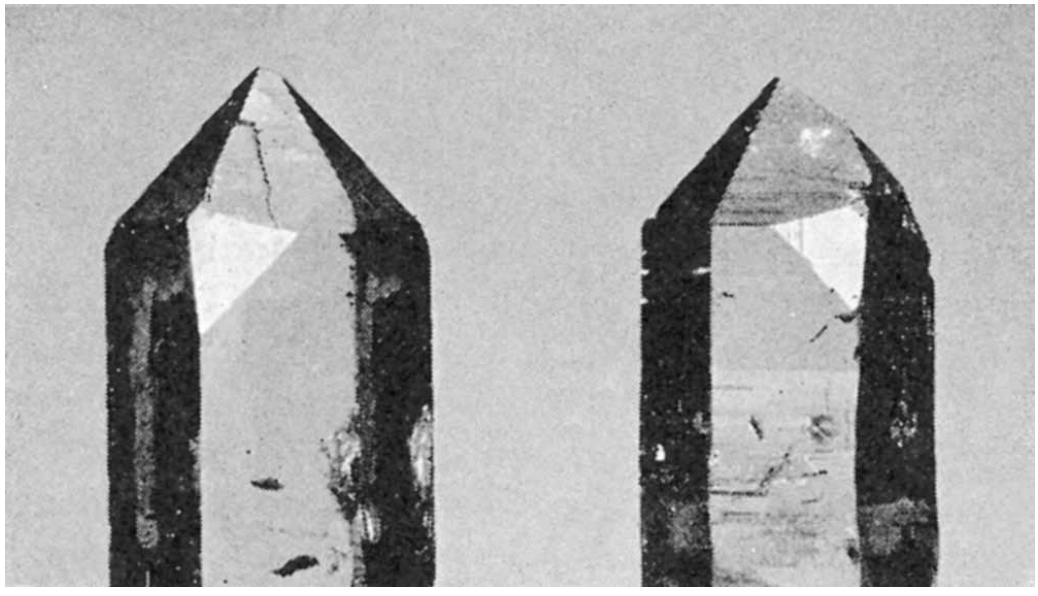

Fig. 1

human intelligence, a left and a right hand and two enantiomorphous tetrahedra.

To grasp the essence of chirality, it is instructive to withdraw for a moment from the familiar three-dimensional world into a two-dimensional one, into a plane, and enquire what chirality means there. In doing this, we are following in the footsteps of E. A. Abbot, who published his well-known science fiction book "Flatland" about 70 years ago. The simplest chiral figure in "Flatland" is an irregular triangle, a scalene. A scalene can be located in a plane in two different ways so that it displays one or other of its two opposite faces. Two equal scalenes "oriented" differently in a plane cannot be brought into congruence by translation or rotation in two-dimensional space but only by reflection across a straight line, the mirror of "Flatland". They are two-dimensionally enantiomorphous. This holds for any triangle where the vertices are distinctly identified.

Let us now consider an intelligent chiral "Flatlander" who can distinguish right and left and who carries on his front side a device which allows him to receive signals from the identifiable vertices ABC of the two triangles, which are for him not transparent (Fig. 3). He will perceive the signals of the first (colorless) triangle in the sequence ACB, CBA, BAC and from the second (black) one in the sequence ABC, BCA, CAB. Thus he will be able to distinguish the two enantiomorphs. However, if one takes them into three-dimensional space they will become indistinguishable. Their nonequivalence gets lost in three-dimensional space.

A planar geometrical figure with more than three vertices can be decomposed into a set of triangles and it can be reconstructed from a set of triangles. Two two-dimensionally chiral triangles can be combined together in a plane in two different ways (Fig. 4). If they display the same face the combination is chiral. If their faces are different the combination can be made – depending on

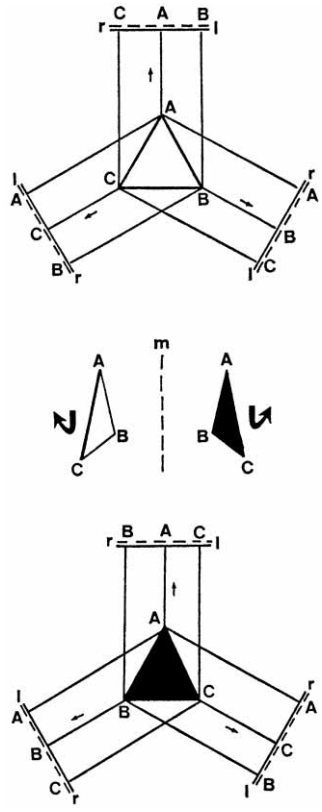

Fig. 3

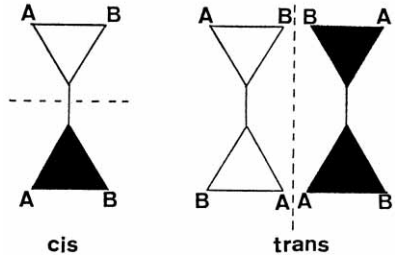

Fig. 4

Fig 2

the symmetry of the combination operation – composite achiral. The two combinations, the chiral and the achiral one, cannot be made congruent, neither by translation and/or rotation nor by reflection; neither in two- nor in three-dimensional space. We call them diastereomorphous or diastereomorphs. Diastereomorphism is not lost in higher dimensions. Thus: chirality is a geometrical property. Enantiomorphism is due to the "orientability" of an object in an "orientable" space. Diastereomorphism is the result of the "mutual orientation" of at least two chiral objects.

These conclusions are valid not only for two-dimensional space but also for spaces of higher dimensions, *e.g.* our three-dimensional perceptual space, apart from the mathematically trivial limitation that we are not actually

able to leave our three-dimensional world – at least the great majority of us.

Familiar planar objects in the two-dimensional information space are capital block letters (Fig. 5). Some of

Fig. 5

them such as A, B, C are two-dimensionally achiral, the others *e.g.* F, G, J... are chiral; they cannot be brought in a plane into congruence with their mirror images. In the following discussion these three types of capital block letters will be used to represent all kinds of two- and three-dimensionally achiral and chiral objects and the enantiomorphs of the latter. In the text the somewhat inconvenient mirror image letters will be replaced by barred ones: $\overline{\mathbf{F}}$, $\overline{\mathbf{G}}$, $\overline{\mathbf{J}}$... *e.g.* the shorthand representation for a scalene of for a chiral tetrahedron will be the letter F and for its enantiomorph $\overline{\mathbf{F}}$. The chiral combination of two triangles or tetrahedra will be represented by F-F or $\overline{\mathbf{F}}$—$\overline{\mathbf{F}}$, the achiral one by **F**—$\overline{\mathbf{F}}$.

But let us now switch over to the second part of the title of my lecture – to the chemistry. Chemistry takes a unique position among the natural sciences for it deals not only with material from natural sources but creates the major part of its objects by synthesis. In this respect as stated many years ago by Marcelin Berthelot, chemistry resembles the arts, the potential of its creativity is terrifying.

Although organic chemistry overlaps with inorganic chemistry and biochemistry it concentrates on compounds of the element carbon. So far, about 2 million of organic compounds are registered with innumerable reactions and interconversions, but the number of compounds obtainable by existing methods is astronomic.

Aldous Huxley writes in an essay: "Science is the reduction of the bewildering diversity of unique events to manageable uniformity within one of a number of symbol systems, and technology is the art of using these symbol systems so as to control and organize unique events. Scientific observation is always viewing of things through the refracting medium of a symbol system and technological praxis is always handling of things in ways that some symbol system has dictated. Education in science and technology is essentially education on the symbolic level". If we agree with Huxley, one of the most important aims of organic chemistry is to develop an efficient symbol or model system. Because biochemistry and biology use the same symbol system when working at the molecular level, every progress in this direction is also a progress of these sciences.

In spite of the great number of known and possible facts, chemistry has succeeded in developing in less than 10^{10} s (*i.e.* 200 years), a system which allows it to keep the "bewildering diversity of events" under control. Compared with the total evolution time of 10^{17}s (3 billion years) this is a remarkably short time, almost a miracle. If the system sometimes does not work perfectly the occasional flaws add to the appeal of organic chemistry for experimentalists and theoreticians in challenging them to improve it.

How does this symbol system work? Organic chemists are mainly interested in pure compounds, *i.e.* substances which consist of only one molecular species. In polymer chemistry, where this is sometimes not possible, we have to be content to work with compounds built from the same building blocks in a uniform manner. The first important information the organic chemist searches for in a compound is the composition or molecular formula *i.e.* the kind and number of atoms in the molecule. The second step is to determine the constitution, *i.e.* which atoms are bound to which and by what types of bond. The result is expressed by a planar graph (or the corresponding connectivity matrix), the constitutional formula introduced into chemistry by Couper around 1858. In constitutional formulae, the atoms are represented by letters and the bonds by lines. They describe the topology of the molecule. Compounds which have the same molecular formulae but different constitution are called isomers. In the late sixties of the last century it was clear that compounds exist which have the same constitution but different properties. One of my predecessors in Zürich, Johannes Wislicenus, expressed the implications of this in a prophetic sentence: "Die Tatsachen zwingen dazu, die verschiedenen Molecüle von gleicher Strukturformel durch verschiedene Lagerung der Atome im Raume zu erklären". The prophecy was fulfilled a few years later when, almost simultaneously, a young Dutchman, Jacobus Hendricus van't Hoff (22), and a young Frenchman, Joseph Achilles Le Bel (27) came out with some simple but novel ideas about the "position of atoms in space". These ideas comprised concepts such as asymmetric atom, free rotation *etc*. Van't Hoff also introduced regular tetrahedra as atomic models from which molecular models could be constructed. This contributed substantially to the rapid propagation of these ideas about chemistry in space, called stereochemistry by Victor Meyer, another of my predecessors in Zürich. The different compounds having the same constitution were called by him stereoisomers, and he distinguished enantiomorphous stereoisomers, enantiomers, and diastereomorphous ones which he named diastereoisomers.

Let us illustrate this by using as example an antibiotic isolated in our laboratories and named boromycin. This is a compound of medium complexity and has the molecular formula $C_{45}H_{74}O_{15}BN$ (Fig. 6). The van't Hoff-

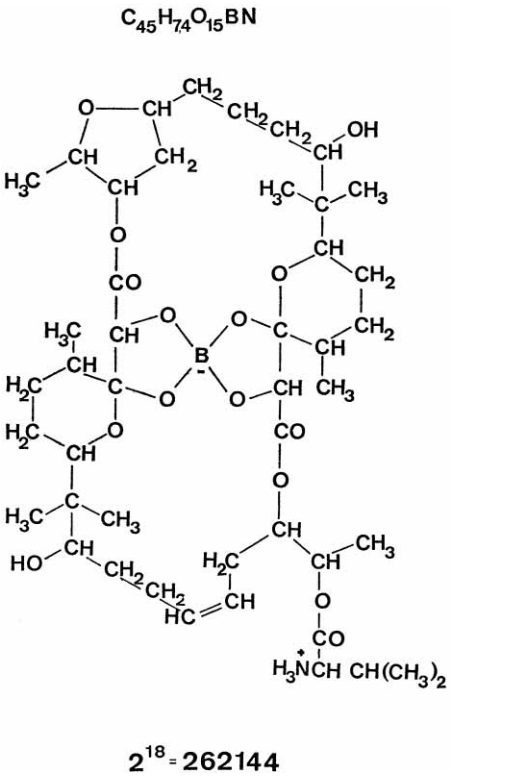

Fig. 6

Le Bel model system allows an average student of chemistry to calculate that the constitutional formula of boromycin corresponds to 262,144 (=2^{18}) stereoisomers. This is a rather large number, compared with the 2 million organic compounds which have hitherto been isolated or synthesized by thousands of hard-working chemists during almost two centuries. If a chemist were to set off to synthesize boromycin, he would not get very far from a knowledge of its constitutional formula alone. To approach his goal, he has to know what is the invariant part of its spatial architecture. Moreover, he has to know processes, stereospecific reactions, which produce specifically the desired stereoisomers and not randomly all possible ones.

One problem in dealing with the multiplicity of stereoisomers is that of communication – how to transfer the information about their molecular architecture in space. This can be done, of course, by three-dimensional models (or their projections) constructed on the basis of coordinates obtainable by diffraction methods *e.g.* by X-ray crystal structure analysis. Such models that describe the complete molecular topography are invaluable for any detailed discussion of the molecules. However, they often include many structural details that are unnecessary for our purpose, *i.e.* specification of the particular stereoisomer. Indeed, some of these details may be dependent on the state (solid, liquid, vapour, solution) in which the molecule was observed. The very abundance of this information often makes it difficult to recognize, register, and memorize that invariant aspect of the topography, the so-called primary structure, which is essential for specification and synthesis of the compound.

In 1954 I joined R. S. Calm and Sir Christopher Ingold in their efforts to build up a system for specifying a particular stereoisomer by simple and unambiguous descriptors which could be easily assigned and deciphered. This system, which now carries our names, makes it possible to convey the essential information with the aid of a few conventions, letter symbols or numbers. In the rather complex model of boromycin (Fig. 7) which contains 136 atoms corresponding to 408 coordinates the primary structure is specified by 18 descriptors. They are:

2R,	3R,	4R,	7S,	9S,	15S,	16R,	22R,	2'R,	3'R,	4'R
0	0	0	1	1	1	0	0	0	0	0

7'S,	9'R,	13'R,	15'S,	16'R,	B R;	12,13	seq	cis
1	0	0	1	0	0		(0)	

The letter symbols used in our system always occur in pairs (*R*, *S*; *M*, *P*; *cis*, *trans*) and hence they can be replaced by the numbers 0 and 1. If these numbers are ordered by using the conventional constitutional sequence of the atoms, we obtain a binary number, which can then be expressed in decimal form *e.g.* for boromycin by (0)00100100000111000 → 18488. From this number the invariant part of the molecular architecture can easily be retrieved.

In the course of building up and improving our system, many problems emerged with regard to the basis of stereoisomerism and the fundamental concepts of stereochemistry. It was soon evident that by specifying most of the stereoisomers, especially those which were called optical isomers, one specifies their total or partial three-dimensional invariant chiralities. Somewhat later it was recognized that *cis-trans* isomerism (sometimes misleadingly called "geometrical" isomerism) is a two-dimensional diastereomorphism. For years, the important role of two-dimensional chirality had been hidden behind a

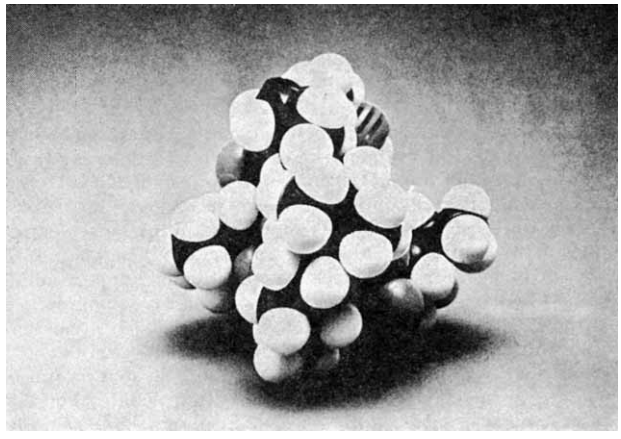

Fig. 7

variety of concepts and words, such as pseudoasymmetry, stereoheterotopy, prochirality, propseudoasymmetry, retention and inversion of configuration, *etc*. All these partially mysterious concepts can be illuminated by regarding them as manifestations of two-dimensional chirality.

The question "What about one-dimensional chirality, the chirality of Lineland?" can be easily answered. The enantiomorphism of Lineland already is lost in Flatland, and the diastereomorphs of Lineland must have different constitutions in one-dimensional space and are therefore not stereoisomers by definition.

Summarizing and extrapolating, one can claim that the duality inherent in the invisible, intangible two- and three-dimensional chiralities of stable molecules or of their parts is the geometrical basis of all stereoisomerism. Such an uniform point of view towards stereochemistry is not only gratifying for theoretical reasons but has also a heuristic value.

Ever since van't Hoff introduced the regular tetrahedra as a model of the carbon atom, chemists have been solving their daily stereochemical problems by inspection of molecular models. The exhaustive exploration of the possibilities of such models (which are essentially geometrical figures) allowed them to answer practically all questions with regard to the number and symmetry of stereoisomers encountered in their work. A good example is Emil Fischer's classical elucidation of the enigmatic diversity of sugars and their derivatives by applying van't Hoff-Le Bel ideas. This is nicely illustrated by the following paragraph from Fischer's autobiography: "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 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 Wiirzburg by long and careful inspection of good models did I succeed in finding the final solution".

Because of the indubitable success of "playing" with models, stereochemistry developed mainly as a pragmatic science. Several attempts to give it a more theoretical background, by F. M. Jaeger, G. Polya, J. K. Senior, E. Ruch, to mention only a few pioneers, had little influence on the experimentalists in the field.

If one tries to develop a universal system for specification of stereoisomers, as we did, it is somewhat embarrassing to find that one does not actually know what types of steroisomers are possible. During the century which had elapsed since the foundation of stereochemistry several types of stereoisomers were discovered, always as a kind of surprise. To mention only a few: the atropisomerism of polyphenyls and of ansa-compounds, due to the so-called secondary structure, *i.e.* hindered rotation around single bonds, "geometrical enantiomorphic" isomerism, *etc*. How many novel types still remained to be discovered? This question is especially relevant when one considers more complex classes of molecules that have not been so thoroughly investigated.

Several years ago Hans Gerlach and I discovered one such novel type, cyclostereoisomerism. Head-to-tail combination of equal numbers of enantiomeric building blocks such as (ABF) and (**AB$\overline{\mathbf{F}}$**) (represented in the following figs, by black and white dots) can lead to cyclic molecules which are either achiral or chiral, depending on the symmetry of the building pattern. Such patterns for the total number of building blocks $n \neq 4$, 6 and 8 are shown on Fig. 8. For one pattern with $n = 6$, two enantiomers are possible with different "sense" of the ring (Nos. 2 and 3). We call these cycloenantiomers. There are two pairs of cycloenantiomers with $n = 8$ (Nos. 2, 3 and 7, 8). With $n = 10$ (Fig. 9) there are already 6 pairs of cycloenantiomers, but in addition to patterns which lead to cycloenantiomers others can be found that give diastereomers on changing the "sense" of the ring (Nos. 4, 6; 5, 7; 12, 14 and 13, 15); these are called cyclodiastereomers. Both types of cyclostereoisomers can be realized in the cyclopolypeptide series. For example, by cyclization of the corresponding penta-alanyl-alanines, two enantiomeric cycle-hexa-alanyls can be obtained, as shown on Fig. 10. With increasing number of building blocks, the number of possible stereoisomers increases considerably: with 15 pairs of enantiometric alanines 5,170,604 stereoiso-

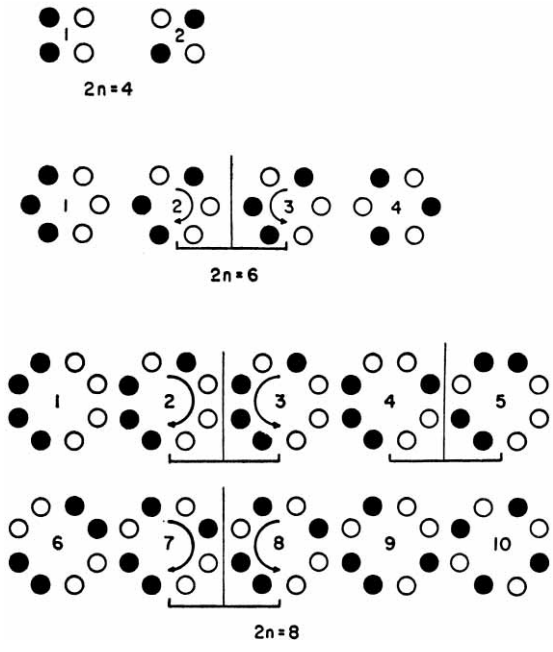

Fig. 8

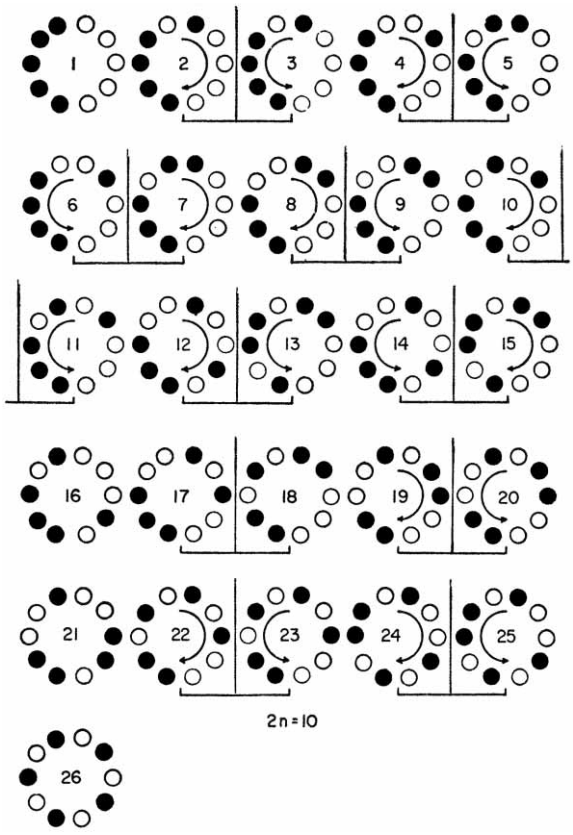

Fig. 9

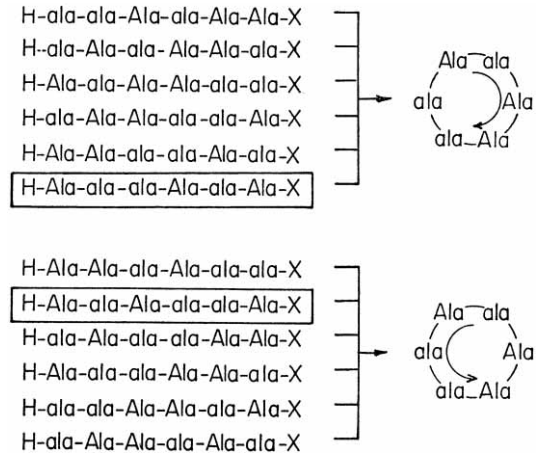

Fig. 10

metric cycle-trikosa-alanyls are possible with the same constitutional formula.

With this in mind, we thought that it might be useful to build up a catalogue of models, based on chirality, which would enable us not only to classify the known stereoisomers but also explore the extent of our present knowledge of stereoisomerism in certain areas.

By showing how to construct one rather trivial page of such a catalogue I may manage to illustrate the general principles. First, all possible different combinations of achiral and chiral objects, including the enantiomorphs of the latter, are selected with the help of partition diagrams, as shown on Fig. 11 for number four. In partition diagrams equal objects are in horizontal rows, unequal ones in vertical columns. If the objects in question are parts of molecules we call them ligands. By occupying vertices of a polyhedron, in our case a regular tetrahedron, with all combinations of ligands, models are obtained which, according to their symmetry, can be divided into two classes: achiral and chiral. An additional classification into two subclasses is possible by introducing the criterion of permutability. Some of the models do not change if two ligands are permuted, the others are transformed by such a permutation either into their enantiomorphs or diastereomorphs.

Among the achiral models obtained by this procedure. Nos. 5 and 6 shown on Fig. 12 are noteworthy because they are models of so called prochiral and propseudoasymmetric atoms; Nos. 7 and 8 are models of pseudoasymmetric atoms.

The enantiomorphs of chiral models on Fig. 13 are shown only if they arise by exchange of ligands, as in

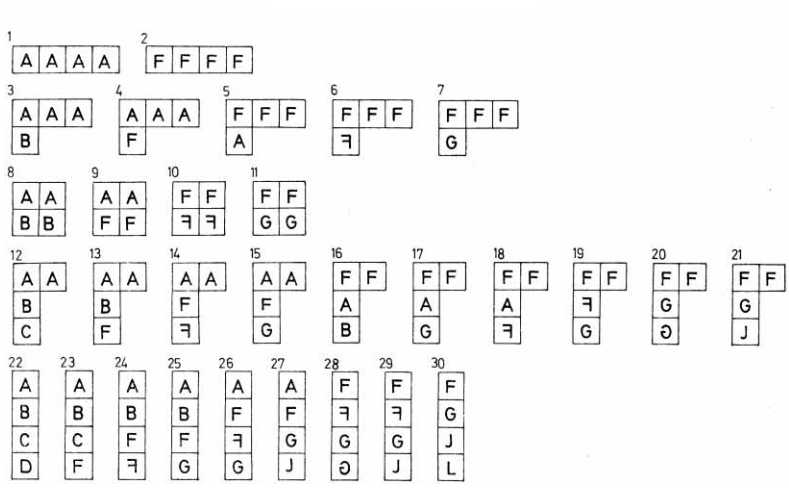

Fig. 11

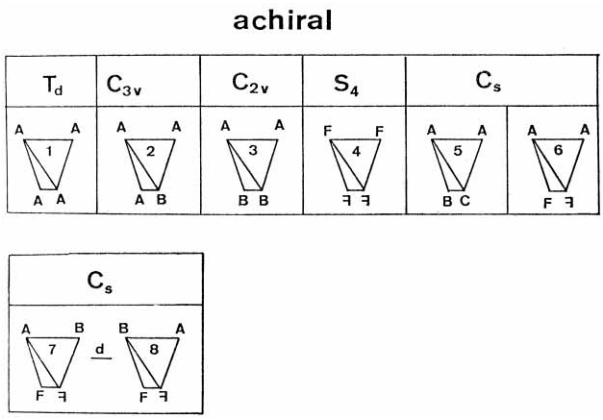

Fig. 12

Nos. 24, 25 and 32, 33. Nos. 24 and 25 are models of the classical "asymmetric atom", the most familiar member of the subclass of "atoms" which are not invariant to permutation (Nos. 24-39).

If one considers that stereochemists have "played" with tetrahedra for more than a century, it is hardly surprising that this catalogue page contains only models of familiar stereoisomers. However, some generalizations are possible. Tetrahedral asymmetric atoms are also called centers of asymmetry or chirality, but such centers are not necessarily occupied by an asymmetric atom (Fig. 14). They can be occupied by atoms with rotational symmetry or the asymmetric atom can be replaced by a rigid atomic skeleton with tetrahedral symmetry such as the

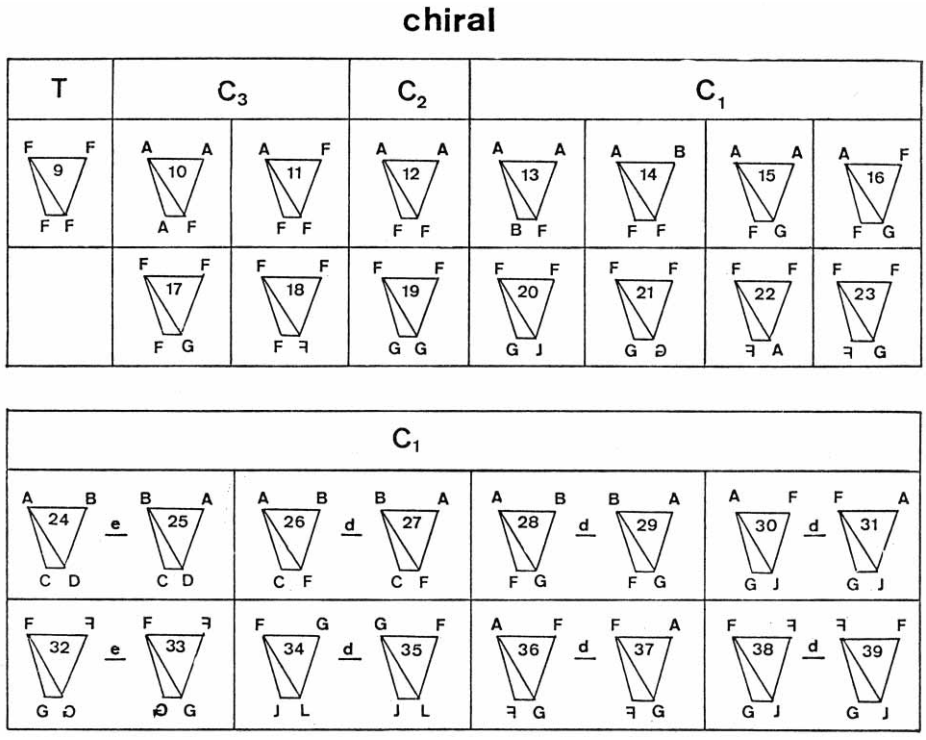

Fig. 13

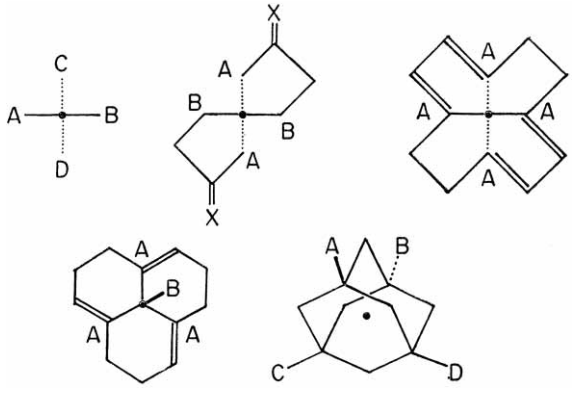

Fig. 14

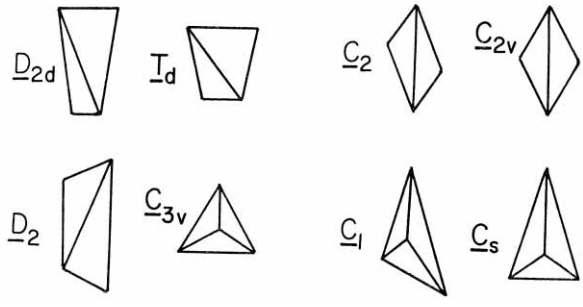

Fig. 15

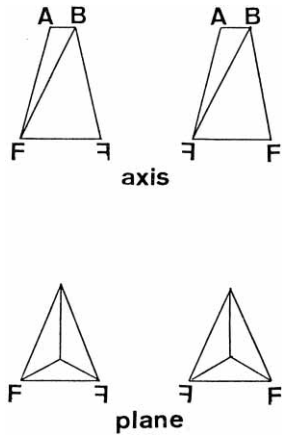

Fig. 16

adamantane skeleton. The centre of the achiral skeleton of adamantane is a center of chirality which is not occupied by an atom.

Van't Hoff had already noticed that there are chiral molecules without centers of chirality and had postulated that allenes with the constitutional formula (AB)C = C = C(AB) are chiral. Models for such cases can be constructed by using as the basic geometrical figure tetrahedra of lower symmetry than that of a regular tetrahedron. Eight point-group symmetries (shown on Fig. 15) are possible for a tetrahedron. Three of them (D_2, C_2 and C_1) are intrinsically chiral *i.e.* their chirality does not depend on how ligands occupy their vertices. The regular tetrahedron (T_d) itself and four others are achiral (D_{2d}, C_{3v}, C_{2v} amd C_s). By occupying the vertices of such tetrahedra with all combinations of four ligands new pages of the catalogue are obtained. These new pages contain some types of stereoisomerism which had escaped the notice of pragmatic stereochemists

I should like to mention only generalized pseudoasymmetric cases with pseudoasymmetric axes and planes, models of which are shown in Fig. 16. Examples of stereoisomeric molecules represented by these models have been prepared by Günter Helmchen in our laboratory (Fig. 17 and 18). It is noteworthy that many bilateral organisms including men are examples of planar pseudoasymmetry.

I have limited the discussion to three-dimensional basic figures with 4 ligands because they are typical for organic stereochemistry. The same procedures can be applied to produce catalogues based on figures with five or more vertices but the multiplicity of models so obtained is larger and therefore more difficult to deal with in a lecture.

The time at my disposition also does not permit me to deal with the manifold biochemical and biological aspects of molecular chirality. Two of these must be mentioned, however, briefly. The first is the fact that although most compounds involved in fundamental life processes, such as sugars and amino acids, are chiral and although the energy of both enantiomers and the probability of their formation in an achiral environment are equal, only one enantiomer occurs in Nature; the enantiomers involved in life processes are the same in men, animals, plants and microorganisms, independent on their place and time on Earth. Many hypotheses have been conceived about this subject, which can be regarded as one of the first problems of molecular theology. One possible explanation is that the creation of living matter was an extremely improbable event, which occured only once.

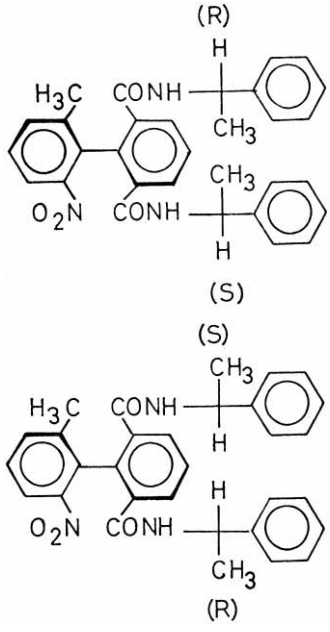

Fig. 17

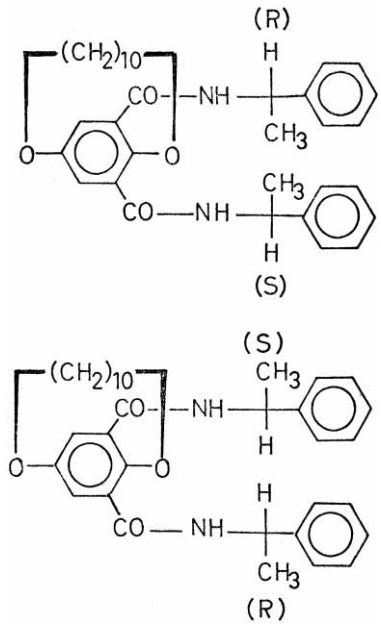

Fig. 18

The second aspect I would like to touch, the maintenance of enantiomeric purity, is less puzzling but nevertheless still challenging to chemists. Nature is the great master of stereospecificity thanks to the *ad hoc* tools, the special catalysts called enzymes, that she has developed. The stereospecificity of enzymic reactions can be imitated by chemists only in rare cases. The mystery of enzymic activity and specificity will not be elucidated without a knowledge of the intricate stereochemical details of enzymic reactions. The protagonist in this field is John Warcup Cornforth.