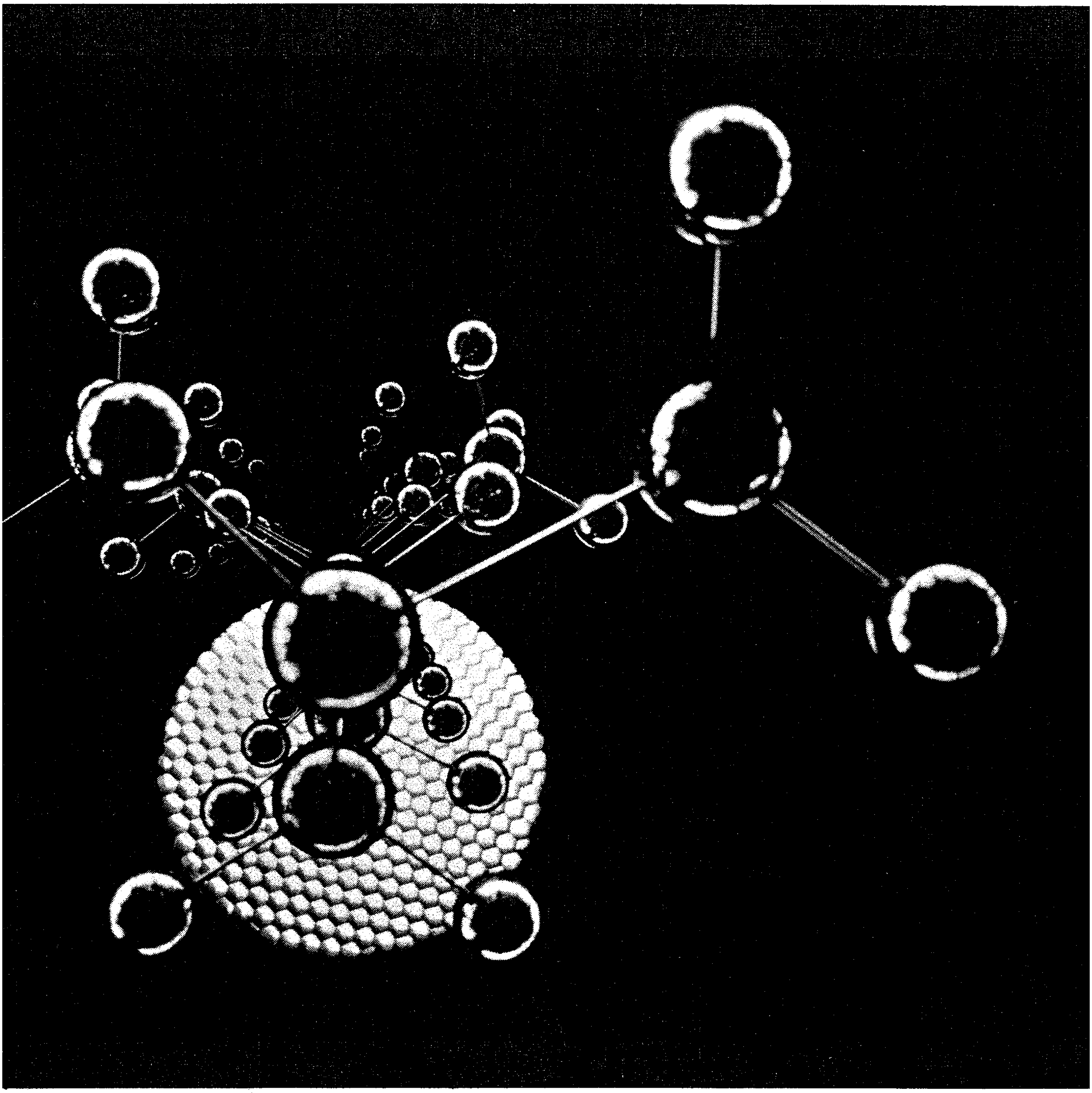
STEREO CHEMISTRY



G. Natta and M. Farina

Stereochemistry

GIULIO NATTA AND MARIO FARINA

Translated by Andrew Dempster

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Appendices

Translator's preface

This book is a translation of *Stereochimica – Molecole in 3D* published in Italian in 1968. The authors have added two new sections and made a number of minor alterations to the original text and these have been incorporated in this English edition. I have tried to follow the Italian text as closely as possible without altogether losing the style of the authors.

I would like to thank Professor Mario Farina for inviting me to make the translation and for his help with various problems which arose in the work.

ANDREW DEMPSTER

December 1970

Preface

This book contains a short history and account of stereochemistry: the study of the three-dimensional structure of molecules and of the relationships between the structure and properties of matter. This subject seems to us to make a particularly suitable introduction to the most important chemical problems of today. The successes of modern chemistry (by modern we mean the chemistry of the last 30-40 years) are directly related to the development of new theories of the forces which bond atoms to each other, and to the appearance of new, rapid and effective methods for the investigation of molecular structures. These factors have produced in the most recent generation of chemists a new sensibility in which stereochemical aspects are useful not only for explaining a limited number of phenomena but also form a basis for the correct interpretation of the reactivity and properties of molecules. If one tries to enter into the heart of chemical phenomena, in particular if one wishes to take steps towards understanding the chemistry of the processes of life, it is necessary to seek the aid of the methods of stereochemistry in large measure; it is necessary to think in three-dimensional terms.

Stereochemistry is not, however, a treatise or a text on stereochemistry. It is neither complete nor systematic, characteristics which we have preferred to neglect in our search for easily understandable, interesting material.

This book was written for a wide public but for one with some chemical knowledge – high school or university – and one of its intentions is to fill an interdisciplinary gap. The language of the chemist is very often incomprehensible to the physicist or biologist (and *vice versa*), largely because of the elementary level of the instruction and the haste in which it is received. The more serious the problem, the greater is the necessity for joint, or at least integrated, work. An attempt to bridge this gap seems to us quite in order. If this book is well received by our chemical colleagues and is useful to them as well, we shall certainly not feel that we have failed.

Written between the beginning of 1966 and the summer of 1967, the text was revised and enlarged in July 1968. This revision allowed us, amongst other things, to introduce some interesting results recently obtained in our laboratories.

One cannot think of a scientific development detached from the men who caused it. For this reason we have frequently cited in the text the names of those who have contributed most to the development of modern stereochemistry. To them and to many others who are not explicitly mentioned we pay homage. We wish to emphasize that the research described in chapter VI, especially concerning the stereospecific polymerizations, is the result of an entire school. To all those who have collaborated we express our deepest gratitude.

GIULIO NATTA
MARIO FARINA

Milan, July 1968

When the editor suggested to me three years ago that I should write a book on stereochemistry, I welcomed the idea with great pleasure and with the intention of giving the work a very large personal contribution. But other duties have made such unending demands on my time in recent years that I have not been fully able to carry this out. If this volume now sees the light of day, the main credit goes to my collaborator, Mario Farina, who has carried out a major part of its drafting and whom I publicly thank here.

GIULIO NATTA

Milan, July 1968

I

Stereochemistry from Pasteur to today

At the age of twenty-six, Louis Pasteur made the first of the numerous discoveries that were to make him one of the greatest chemists and biologists of the last century. It was the year 1848, and we do not know if the revolutionary wind which was blowing over the whole of Europe also stirred the studious young man of the École Normale in Paris. We do know, however, that his intuition, his capacity for observation and his experimental accuracy made a revolution also and created a new science.

It is almost impossible to evaluate later in time the human and intellectual difficulties of a given enterprise. Only the person who has attempted to venture into the unknown, the mountaineer or the scientist, knows that everything is easy in repetition: on the first occasion one gropes in the dark, scaling the wall without support, searching for an unforeseen result; the road opens only through investigation at ones own physical or intellectual risk. Often years of work are required before the facts become clear, and a rational, satisfying explanation is found. In this case, another twenty-six years were required before Jacobus van't Hoff succeeded in interpreting Pasteur's findings in a definite manner by constructing a three-dimensional theory of organic compounds.

But let us return to the beginning. The first half of the nineteenth century was the great age of geometrical optics: the phenomena of diffraction, interference and the polarization of light were studied in depth by numerous scientists of the French school, such as Fresnel, Malus, Biot and Arago. In particular, the study of linear polarization and of the rotation of the plane of polarization very quickly attracted attention, because of the obvious relationships between these phenomena and the structure of matter.

According to wave theory, light can be considered as an electromagnetic vibration propagated at a tremendous velocity (300000 km/s) in a straight line. The electric and magnetic fields oscillate in a direction perpendicular to each other and to the direction of the

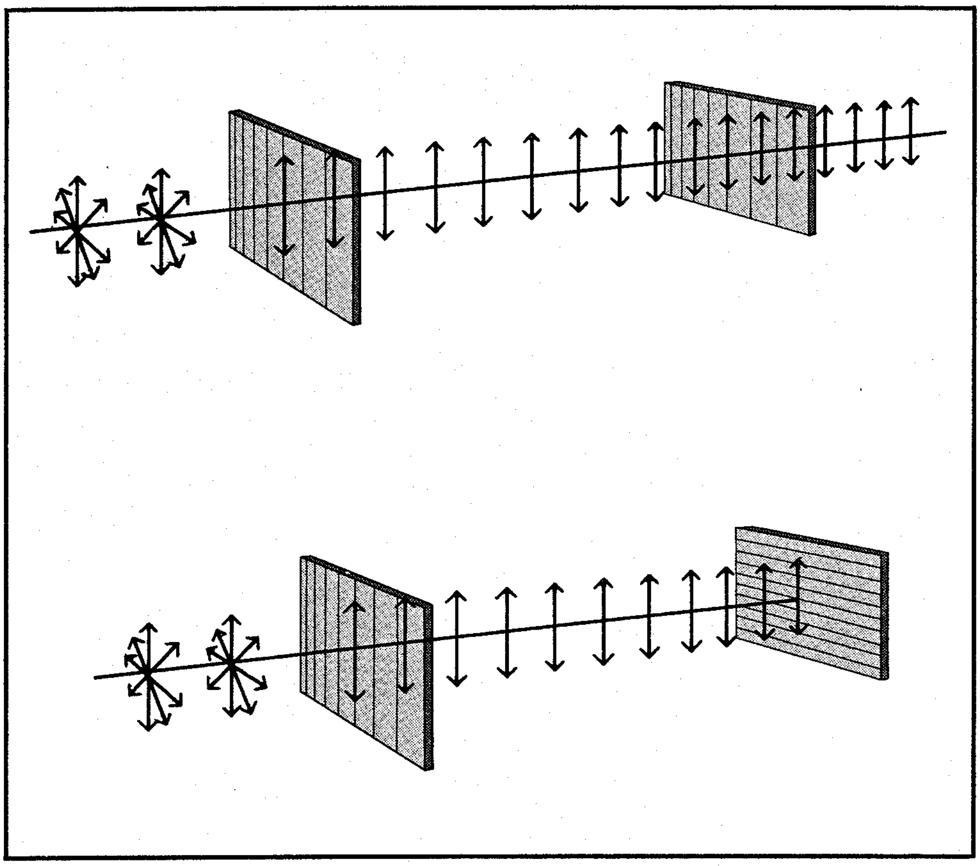


Fig. 1 When a ray of light passes through a Nicol prism or a sheet of Polaroid the light becomes linearly polarized, i.e., it possesses a fixed, well-defined plane of vibration. A second polarizer parallel to the first allows the light to pass through it but if the second polarizer is perpendicular to the first the light is completely extinguished.

ray, setting up periodic waves the length of which, in the case of visible light, determines the colour of the ray. In linearly polarized light, which is usually obtained by means of a Nicol prism, the plane of vibration of the electric field is fixed (Fig. 1). The human eye cannot distinguish polarized light from normal light, but the phenomenon can be made evident with a second polarizer; with Polaroid spectacles for example. The car driver or the lakeside fisherman knows that the annoying reflections of the sun are eliminated with these spectacles and that a simple inclination of the head is enough to make the reflections appear or disappear. By doing this he has used, without knowing it, a system of two polarizers (smooth surfaces of water and asphalt are efficient polarizers in certain conditions) analogous in principle to that used by chemists.

It was soon obvious that certain substances, such as quartz, have the power to cause a rotation of the plane of polarization of light through a definite angle. More exactly, sheets of quartz obtained from certain crystals cause the plane of polarization to rotate towards the right and sheets obtained from other crystals have the opposite effect. A close morphological examination showed that such crystals are not mirror symmetric, that is to say they are not identical to their own reflections in a mirror. The presence of some small, variously orientated faces (hemihedral faces), places the two sorts of crystals in a relationship similar to that existing between a right and a left hand: these are mirror images of each other but

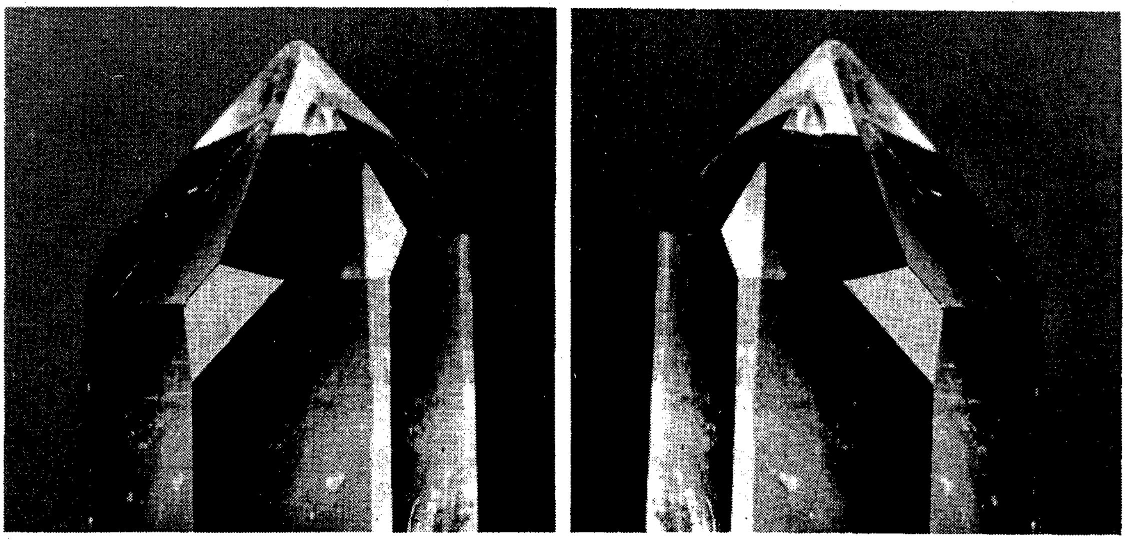


Fig. 2 Two enantiomorphous crystals of quartz. Each is a mirror-image of the other–they cannot be superimposed. To see this comparison better it would be more suitable to examine some ideal crystals; but even in these, the presence of differently orientated hemihedral faces prevents the superposition of the crystals.

neither can be superimposed on the other (Fig. 2). A given crystal of quartz cannot be superimposed on its own mirror image and two different classes of crystals can be distinguished, one of which we shall call right-handed or D and the other left-handed or L. All the right-handed (dextrorotatory) crystals of quartz have the same effect on polarized light, causing its plane of polarization to be rotated towards the right and, analogously, the left-handed crystals (called optical antipodes or enantiomorphs of the first) cause it to be rotated to the left (Fig. 3).

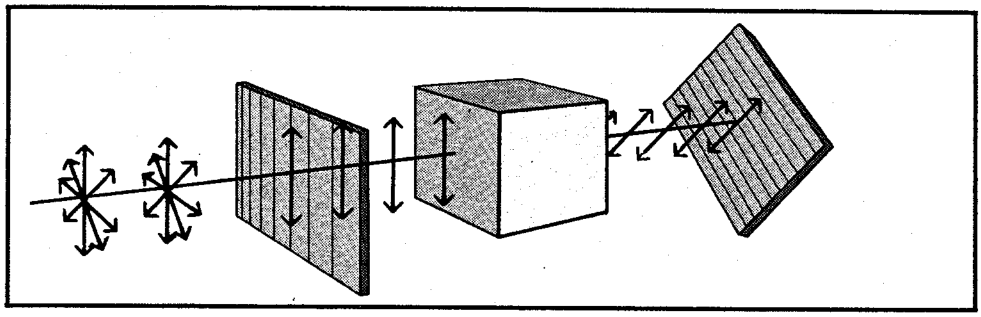


Fig. 3 If a ray of polarized light passes through an optically active substance, the plane of polarization is rotated through a definite angle. The value of the angle of rotation is measured using a second polarizer. The position at which the ray is extinguished is changed with respect to the value obtained in the absence of the active compound. With modern photoelectric polarimeters the angles can be measured with a precision of one ten-thousandth of a degree. The value of the optical activity (or rotatory power) is expressed as specific activity $[\alpha] = \alpha / d . l$, where d is the density of the compound (if it is a pure liquid) or its concentration (if it is a solution) expressed in g/cm^3 and l is the length of the polarimeter tube in decimeters. The rotatory power varies with the temperature and with the wavelength of the light used; thus monochromatic light is used, generally the sodium D line. More accurately, optical activity may be measured at different wavelengths and a graph showing the variation of α as a function of the wavelength λ (an optical rotatory dispersion curve) can then be drawn.

An important relationship was thus established between crystal structure and optical activity (the name given to the phenomenon of the rotation of the plane of polarization of light). But further facts complicate and make the phenomenon much more interesting. With the aid of a simple apparatus called a polarimeter, one can see that certain chemical substances of vegetable or animal origin also show optical activity in the liquid state, in solution, or even in the vapour phase. Spirit of turpentine (obtained from conifers), camphor, and aqueous sugar solutions all produce definitely measurable rotations. To what can this phenomenon be attributed? It certainly cannot arise from the crystal structure, for this was broken up by the effect of temperature or of the solvent: the cause of the phenomenon must be sought at a more elementary level of structure. It is at this point that Pasteur's research intervenes.

Pasteur and the resolution of tartaric acid

Tartaric acid is a by-product of alcoholic fermentation obtained in great quantities from the tartar deposited in barrels. Today it is of some practical interest in the preparation of effervescent drinks. At the time of Pasteur its structure had not been completely determined; it was known to have the formula $C_4H_6O_6$ and to show dextrorotatory optical activity. Pasteur's first observation was of a morphological and crystallographic nature. He saw that the habit of tartaric acid crystals is not symmetric. That is to say that no crystal could be superimposed on its own image obtained by reflection in a mirror. As in quartz, there are hemihedral faces which are always orientated in the same sense. In contrast to quartz, tartaric acid is optically active in solution as well. The idea then came to Pasteur that the asymmetry of the crystal habit might be related to the optical rotation in solution. Following this idea, he examined racemic tartaric acid. This compound, also a by-product of wine production, was already known to have the same chemical composition as dextrorotatory tartaric acid but, in contrast, to be optically inactive. Pasteur took one of its salts and left it to crystallize, hoping to obtain a confirmation of his hypothesis: as the compound was optically inactive, its crystalline form should be symmetric.

But the result was absolutely unforeseen. With the aid of a lens, he was able to observe that each crystal had hemihedral faces but in different crystals they were orientated sometimes to the left and sometimes to the right. With great patience he separated a certain quantity of the two crystalline forms, examined them with the polarimeter and obtained a sensational result. His racemic acid had been separated (today we would say resolved) into two optically antipodal forms, one dextro (right-handed) and the other laevo (left-handed). The two solutions in fact showed opposite rotatory power. The dextrorotatory acid thus obtained was in all respects identical with that previously studied, while the laevo form also had identical chemical and physical properties except for rotatory power. Moreover, if equal quantities of the two optical antipodes were mixed and rapidly crystallized, they gave back the racemic acid.

This discovery was important for many reasons. It showed that certain compounds could exist in enantiomorphous forms each with an opposite effect on polarized light and that other compounds could be inactive because of compensation between laevo and dextro forms present in equal quantities (such compounds are now known as racemates). In addition, the proof of a relationship between optical activity and crystalline asymmetry was obtained. Furthermore, the idea arose that asymmetry is a very fundamental phenomenon of which the crystallographic aspect is only one consequence. It was thus necessary to carry the investigation to more elementary structures; in other words to the molecule itself. But the state of knowledge of chemical structure at that time was too empirical to give an answer to the problem. Pasteur reached the point of postulating an intrinsically dissymmetric structure but could go no further. It was necessary to wait for other knowledge and other men.

It cannot be denied that a fortunate series of circumstances helped Pasteur in his research. The tartrate used by him is one of the very few substances which undergo a spontaneous separation into optical antipodes; moreover, this separation takes place only below 27°C. If Pasteur had worked in a torrid Mediterranean summer rather than at Paris, we would perhaps have in his place the name of another chemist unknown today. However, he clearly showed himself to be worthy of his good fortune. In less than a decade of work in this field, he isolated a fourth type of tartaric acid with structure different from those found previously and which could not be separated into optical antipodes (*meso*-tartaric acid); and he also discovered two further fundamental methods of resolving racemates, both of which are still used today.

The analogy with the right and left hands is again useful. Let us assume that we have two gloves, both being right-handed. One hand will fit easily but the other will not. If we have a right-handed compound, for example, D-tartaric acid, and we cause it to react with a racemic mixture of another compound, for example, an amine (which we shall call D′ and L′), the hand-glove relationship suggests that the D-D′ pair will be favoured with respect to the D-L′. A mirror relationship no longer exists between the two pairs — the mirror images will be respectively L-L′ and L-D′ — but one of *diastereoisomerism*. D-D′ and D-L′ are known as diastereoisomers or diamers and have different solubilities, different melting points, and different speeds of formation and decomposition. In principle, D-D′ and D-L′ may be separated, for example, by fractional crystallization; if they are then decomposed into their constituents, it is possible to obtain the separate D′ and L′ in a more or less pure form.

In 1858 Pasteur published research concerning the action of a mould, *Penicillium glaucum,* on the racemic tartrate. Of the two compounds, the D-tartrate and the L-, the mould destroys the first more quickly, and if the process is interrupted after a certain amount of conversion has taken place, the L-tartrate can be obtained in a fairly pure form. This is a biochemical method of resolution which has a wide variety of applications. Although this process is a variation of the first, it introduces us to another fundamental problem, that of the asymmetry of living organisms.

We have already observed that the first compounds to show optical activity in the liquid state were products of animal or vegetable origin. This is no accident; only living organisms have the capacity to select one of the two optically antipodal forms and this, as in the analogy of the hand and the glove, is precisely because they themselves are asymmetric. The starch and cellulose of plants are made from an asymmetric sugar, glucose. Of the two possible forms of glucose D and L, only the D exists to any appreciable extent in nature. Each of the amino acids from which proteins are made, although potentially capable of existing in two forms, is normally found only in the L form.

If optically active substances exist in nature or in the laboratory, they are related directly or indirectly to living organisms or they are the result of chance separations like that of the tartrates. But in this latter case there will be an equal probability of finding a dextro or laevo form. The problem is too important to deal with fully at this point; it involves the origin of optical activity on Earth and thus, perhaps indirectly, that of the origin of life. We shall discuss it later when our knowledge will be clearer and more complete.

The tetrahedral carbon atom

The first decisive work of unification in organic chemistry was that of the German chemist August Kekulé who realized that the tetravalent carbon atom is the basis of all structures. Between 1858 and 1865 he developed a theory which accounted very well for the structure and behaviour or organic compounds. According to Kekulé's theory the carbon atom is tetravalent in the sense that it can bond with four other atoms, for example with four hydrogen atoms, or with other carbon atoms to produce chains or rings of varying sizes. Chains and rings can have further branches or be connected to other atoms (oxygen, nitrogen, sulpher, etc.) or to groups of atoms, the so-called functional groups (Table I). In almost all of these compounds the tetravalency of carbon is maintained. However, in some compounds carbon can bond to a smaller number of other atoms, that is, can have a lower valency. In these cases the compounds show very typical behaviour: they easily undergo addition reactions, thus leading to the maximum degree of combination. Kekulé formulated these 'unsaturated' compounds with multiple bonds between the atoms, for example, $C{=}C$, $C{=}O$, etc. On addition of two hydrogen atoms one of the two bonds is eliminated and a saturated compound is obtained.

Using Kekulé's theory it became possible to write the structural formulae of organic compounds and, consequently, to divide them into classes depending on the functional groups present in the molecule. Each class (alcohols, acids, amines, etc.) displays its own typical reactivity, but each compound differs in its specific properties, both physical (melting point, boiling point or solubility) and chemical (greater or lesser reactivity towards the same reagent, etc.).

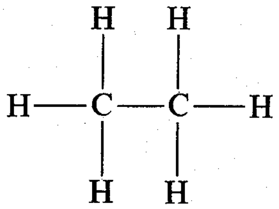
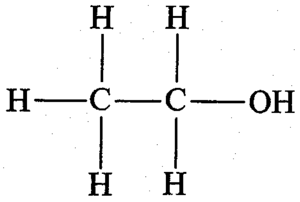
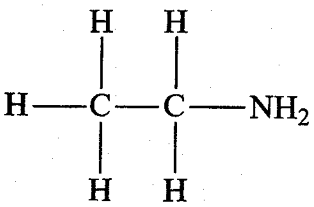
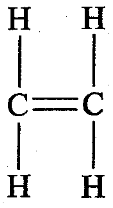
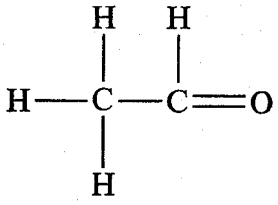
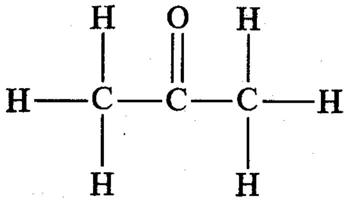
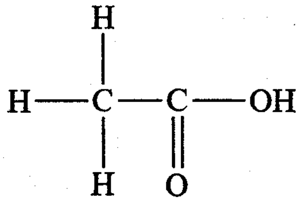
Kekulé's structural theory is the basis of all organic chemistry and it played an important rôle until the arrival of the modern interpretations of chemical valence which are based on a deeper knowledge of atomic phenomena. Only one further step, although a large one, was required to make it capable also of resolving the problems of stereochemistry. This occurred in 1874 from the work of a Dutchman, Jacobus van't Hoff, and a Frenchman, Joseph Achille Le Bel. These two, who were student friends in Paris, reached substantially similar conclusions by independent paths. We will express them in the more complete and better-known form put forward by van't Hoff.

These conclusions can be summarized thus: to obtain a satisfactory explanation of experimental facts, it is necessary to assume that the carbon atom has four valencies arranged in a tetrahedral manner. This hypothesis had, in fact, already been formulated some years before by Emanuele Paternò (Fig. 4) in a note published in Palermo, Sicily, in 1869. (The original text is reproduced in Appendix I, p. 235). But although he had clearly seen the problem, Paternò did not develop all the consequences of his hypothesis and the rational explanation of optical activity in organic compounds must be credited to van't Hoff and Le Bel.

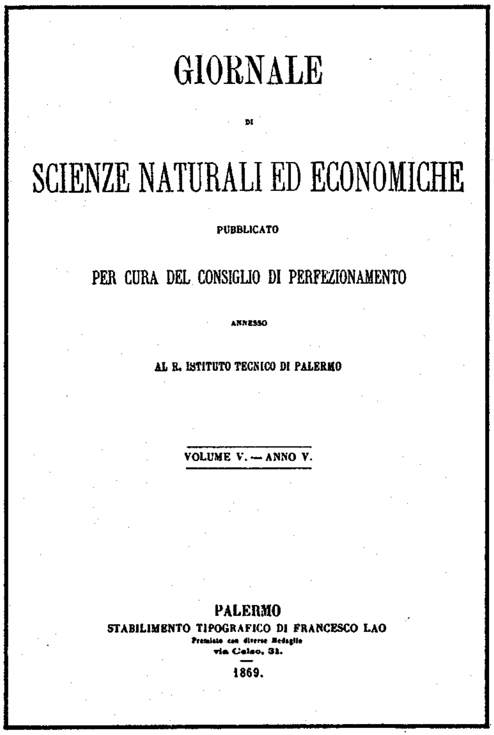
The foundation of classical stereochemistry

At the time of van't Hoff, scarcely more than ten optically active compounds of which the structures had been determined were

Table I. Symbolism and nomenclature of organic chemistry*

 $H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-H$	CH_3-CH_3	**ethane**
 $H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-OH$	CH_3-CH_2OH	**ethyl alcohol**
 $H-\overset{H}{\underset{H}{C}}-\overset{H}{\underset{H}{C}}-NH_2$	$CH_3-CH_2-NH_2$	**ethylamine**
 $\overset{H}{\underset{H}{C}}=\overset{H}{\underset{H}{C}}$	$CH_2=CH_2$	**ethylene**
$H-C\equiv C-H$	$CH\equiv CH$	**acetylene**
 $H-\overset{H}{\underset{H}{C}}-\overset{H}{C}=O$	CH_3-CHO	**acetaldehyde**
 $H-\overset{H}{\underset{H}{C}}-\overset{O}{\overset{\Vert}{C}}-\overset{H}{\underset{H}{C}}-H$	$CH_3-CO-CH_3$	**acetone**
 $H-\overset{H}{\underset{H}{C}}-\underset{O}{\underset{\Vert}{C}}-OH$	CH_3-COOH	**acetic acid**

* The structural formulae of organic compounds are still written today in the manner invented by Kekulé. From the left, the complete structural formula, the abbreviated (most frequently used) formula and the name of the compound.



GIORNALE

DI

SCIENZE NATURALI ED ECONOMICHE

PUBBLICATO

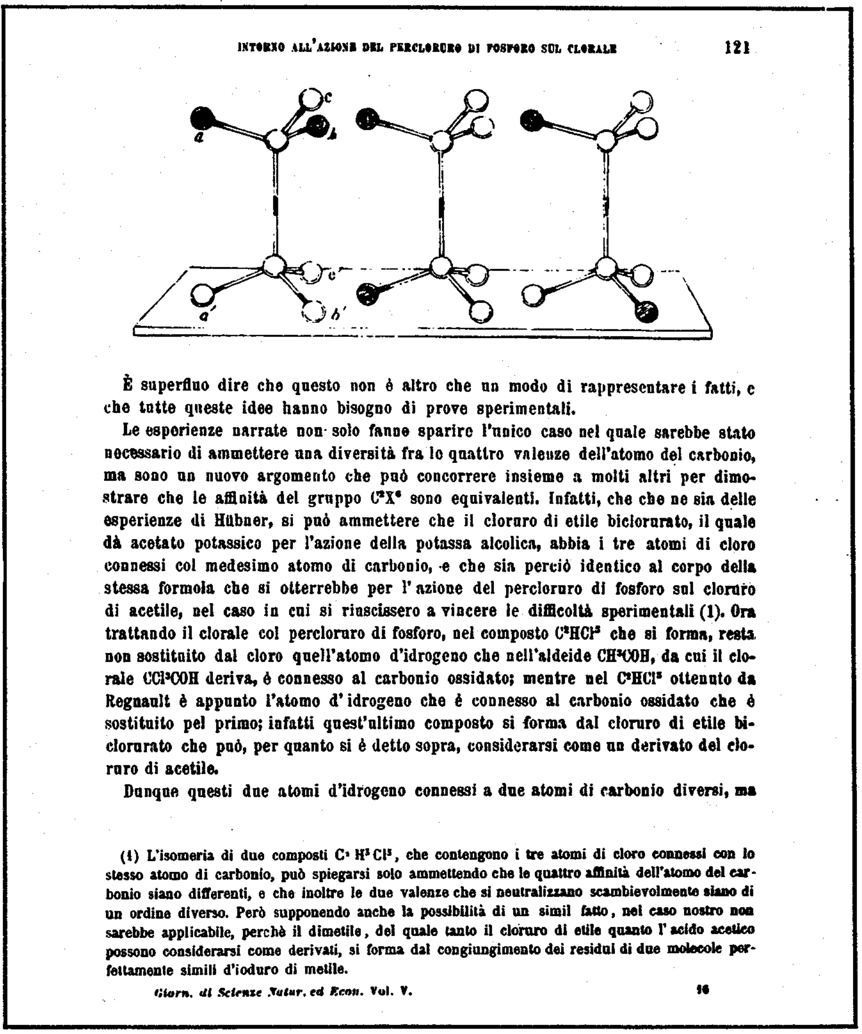
PER CURA DEL CONSIGLIO DI PERFEZIONAMENTO

ANNESSO

AL R. ISTITUTO TECNICO DI PALERMO

VOLUME V. — ANNO V.

PALERMO
STABILIMENTO TIPOGRAFICO DI FRANCESCO LAO
Premiato con diverse Medaglie
via Celso, 31.
1869.



INTORNO ALL'AZIONE DEL PERCLORURO DI FOSFORO SUL CLORALE 121

È superfluo dire che questo non è altro che un modo di rappresentare i fatti, e che tutte queste idee hanno bisogno di prove sperimentali.

Le esporienze narrate non solo fanno sparire l'unico caso nel quale sarebbe stato necessario di ammettere una diversità fra le quattro valenze dell'atomo del carbonio, ma sono un nuovo argomento che può concorrere insieme a molti altri per dimostrare che le affinità del gruppo C^2X^6 sono equivalenti. Infatti, che che ne sia delle esperienze di Hübner, si può ammettere che il cloruro di etile biclorurato, il quale dà acetato potassico per l'azione della potassa alcolica, abbia i tre atomi di cloro connessi col medesimo atomo di carbonio, e che sia perciò identico al corpo della stessa formola che si otterrebbe per l'azione del percloruro di fosforo sul cloruro di acetile, nel caso in cui si riuscissero a vincere le difficoltà sperimentali (1). Ora trattando il clorale col percloruro di fosforo, nel composto C^2HCl^5 che si forma, resta non sostituito dal cloro quell'atomo d'idrogeno che nell'aldeide CH^3COH, da cui il clorale CCl^3COH deriva, è connesso al carbonio ossidato; mentre nel C^2HCl^5 ottenuto da Regnault è appunto l'atomo d'idrogeno che è connesso al carbonio ossidato che è sostituito pel primo; infatti quest'ultimo composto si forma dal cloruro di etile biclorurato che può, per quanto si è detto sopra, considerarsi come un derivato del cloruro di acetile.

Dunque questi due atomi d'idrogeno connessi a due atomi di carbonio diversi, ma

(1) L'isomeria di due composti $C^2H^3Cl^3$, che contengono i tre atomi di cloro connessi con lo stesso atomo di carbonio, può spiegarsi solo ammettendo che le quattro affinità dell'atomo del carbonio siano differenti, e che inoltre le due valenze che si neutralizzano scambievolmente siano di un ordine diverso. Però supponendo anche la possibilità di un simil fatto, nel caso nostro non sarebbe applicabile, perchè il dimetile, del quale tanto il cloruro di etile quanto l'acido acetico possono considerarsi come derivati, si forma dal congiungimento dei residui di due molecole perfettamente simili d'ioduro di metile.

Giorn. di Scienze Natur. ed Econ. Vol. V. 16

Fig. 4 On the right is a reproduction of a page of the *Giornale di Scienze Naturali ed Economiche* (Journal of Natural and Economic Sciences) printed in Palermo in 1869; it is of great historical importance since it gives the first drawing of a tetrahedral carbon atom. The cover of the magazine is reproduced above. A more complete examination of Paternò's original work is given in Appendix I p. 235).

known. All of these compounds were of a particular type in that a carbon atom was bonded to four different substituents (C_{ABDE}). An examination of the possibilities in which four substituents can be arranged around a central carbon atom shows that when the carbon atom is placed at the centre and the four substituents at the corners of a tetrahedron, the existence of structures which are mirror images of each other is possible. The fact that there is only one compound of the type C_{AABB} and C_{AABD} excludes other spatial arrangements such as a square or a rectangular pyramid. An atom of the type C_{ABDE} which gives rise to the existence of two enantiomorphic structures is called an asymmetric carbon atom: it is, in fact, incompatible with the presence of any element of reflective symmetry (Fig. 5).

With his book *La Chimie dans l'Espace,* van't Hoff began to develop the rigorous and logical construction of classical stereochemistry. Starting from a limited amount of data, he succeeded in resolving all the most important structural problems then existing and he predicted further phenomena which were not verified until a good seventy years later (for example, stereoisomerism of the allenes). We know today that the hypotheses of van't Hoff, while being valid, do not go beyond a certain level of interpretation; it was only on the basis of facts then unknown, such as the isomerism of the substituted biphenyls (discovered in 1922) and with the advent of new methods of study and new experimental techniques, that one of his postulates reached a point of crisis and required a new formulation of stereochemistry (which we shall describe in chapters III and IV).

As well as the tetrahedral arrangement of valencies, van't Hoff's theory involved a second principle, that of free rotation about single bonds. As Paternò had already observed, a rigid formulation of structures would lead to the prediction of a number of compounds greater than was actually observed. One must assume that the tetrahedra can rotate around their vertices. If all the forms that can interconvert with these rotations are considered as a single compound, the agreement between experiment and prediction is com-

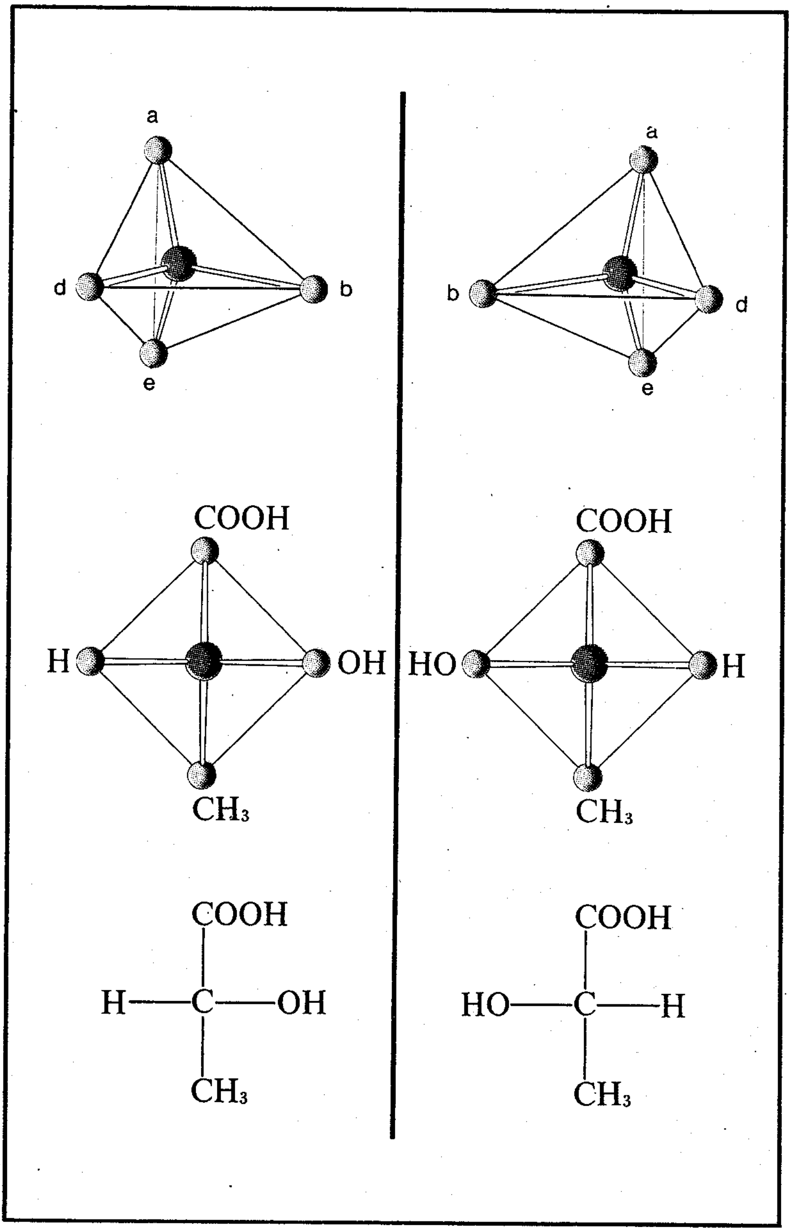


Fig. 5 Only a tetrahedral arrangement of the substituents allows the existence of optical antipodes in compounds of the type C_{ABDE} while ensuring the absence of isomers in compounds of the type C_{AABB}. The figure on the upper left-hand side is the non-superimposable mirror image of the one on the right. With a conventional representation of three-dimensional structures, the tetrahedron is observed from above, after being placed on an edge in such a way that the upper edge appears horizontal in the drawing (centre). By eliminating the outlines of the tetrahedron the Fischer projection of the compound is obtained, in the present case that of negative (on the left) and positive lactic acid. In this projection (below) the vertical valencies are directed below the plane of the paper and the horizontal ones are above it.

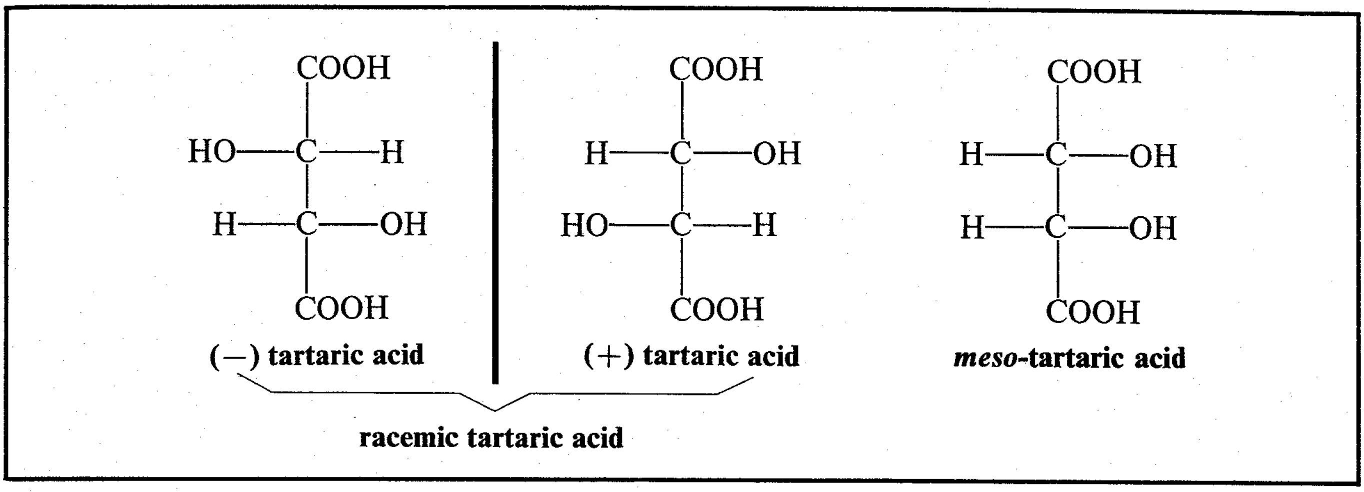


Fig. 6 Formulae in Fischer projection. From the left, (−), (+) and *meso*tartaric acid. The two asymmetric atoms have identical configurations in the first two compounds and opposite ones in the third.

plete. On this basis it is easy to explain, for example, the existence of two optical antipodes of lactic acid, one having the configuration D (that which comes from the fermentation of milk sugar) and the other configuration L (that produced by muscle). The term configuration signifies the arrangement of the various groups in space and uniquely characterizes a given optical antipode.*

We can now re-examine the question of tartaric acid (Fig. 6). In this molecule there are two equal asymmetric carbon atoms (each is bonded to the following atoms or groups of atoms: —H, —OH, —COOH and —CHOH—). If we call their possible configurations D or L, we can write three different combinations: D-D, L-L and D-L (the other possibility L-D being identical to D-L). The first two represent the optically active tartaric acids – one positive and the other negative – and the racemic acid is just their equimolecular mixture. The last combination contains two asymmetric atoms of opposite sign in which the effect is mutually cancelled; this is optically inactive *meso*-tartaric acid. The relationship of D-D (or L-L) tartaric acid to D-L (*meso*) tartaric acid is that of diastereoisomers, or compounds with the same composition but having different spatial structures. The problems raised by Pasteur's research were thus brilliantly resolved, and the stereochemical theory of van't Hoff was shown to be of great potential value. With the fundamental principles now made clear, it was possible to direct research in a rational manner towards the structures of more complex compounds. In this connection the work of Emil Fischer, whose name is closely associated with the chemistry of sugars, was paramount.

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* The nomenclature given here concerns only the configurations and not the experimental rotations: in effect, D-lactic acid has a negative rotatory power and the L-acid positive. For modern conventions on the nomenclature of optical antipodes see Appendix II, p. 239.

The structures of the sugars

Few natural products have an importance in the history of mankind as great as that of the sugars. We say sugars, and not sugar, because more than one type is found in nature. The best known, common sugar from cane or beet, properly called sucrose, is really a disaccharide, a combination of two simple sugars, glucose and fructose. Other sugars of importance include galactose from milk and the well-known ribose and deoxyribose which are components of nucleic acids and are thus intimately connected with the processes of life.

But if we wish to speak about the quantitatively and historically most important sugar, there is no doubt that our attention must be focused on glucose (dextrose). Contained in the free state in grapes and other fruit and as a polysaccharide in starch and cellulose, glucose is a fundamental element of human and animal nutrition. Moreover, from its fermentation, alcohol is obtained in aqueous solution in low proof (wine, beer) or in high proof after distillation. A large part of the terrestrial biological cycle is associated with the production and distribution of glucose (Fig. 7). Photosynthesis, the most important chemical process existing on Earth, ensures its continuous supply; agrarian science is none other than a search for higher yields in this process, taking account of the climate, of the surroundings, and of the requirements of a given human group. Wheat, maize, rice and potatoes are well known sources of starch and if to these are added cotton, hemp, wood pulp (or cellulose), we can appreciate the enormous economic interests that lie behind glucose. It is thus perfectly logical that for a century chemists should have dedicated a major part of their energies and thought to this sugar.

Towards 1885, when Fischer became interested in the problem, the structure of glucose had been only partly determined. Today we know that its empirical formula is $C_6H_{12}O_6$, that in certain aspects it can be considered a compound with a linear structure, and that it shows both aldehydic and alcoholic reactivity. Its structural formula is shown in Fig. 8.

The four non-terminal carbon atoms are all asymmetric and different from each other and one can therefore predict the existence of sixteen ($2 \times 2 \times 2 \times 2$) sugars of this formula. The problem was to discover which of these structures was really that of glucose or, more exactly, that of (+)-glucose. Fischer succeeded after a decade of work and also by risking his own life. (He suffered serious poisoning caused by phenylhydrazine, a compound discovered by him and which had an important place in his research.)

Even a brief description of Fischer's work would require explan-

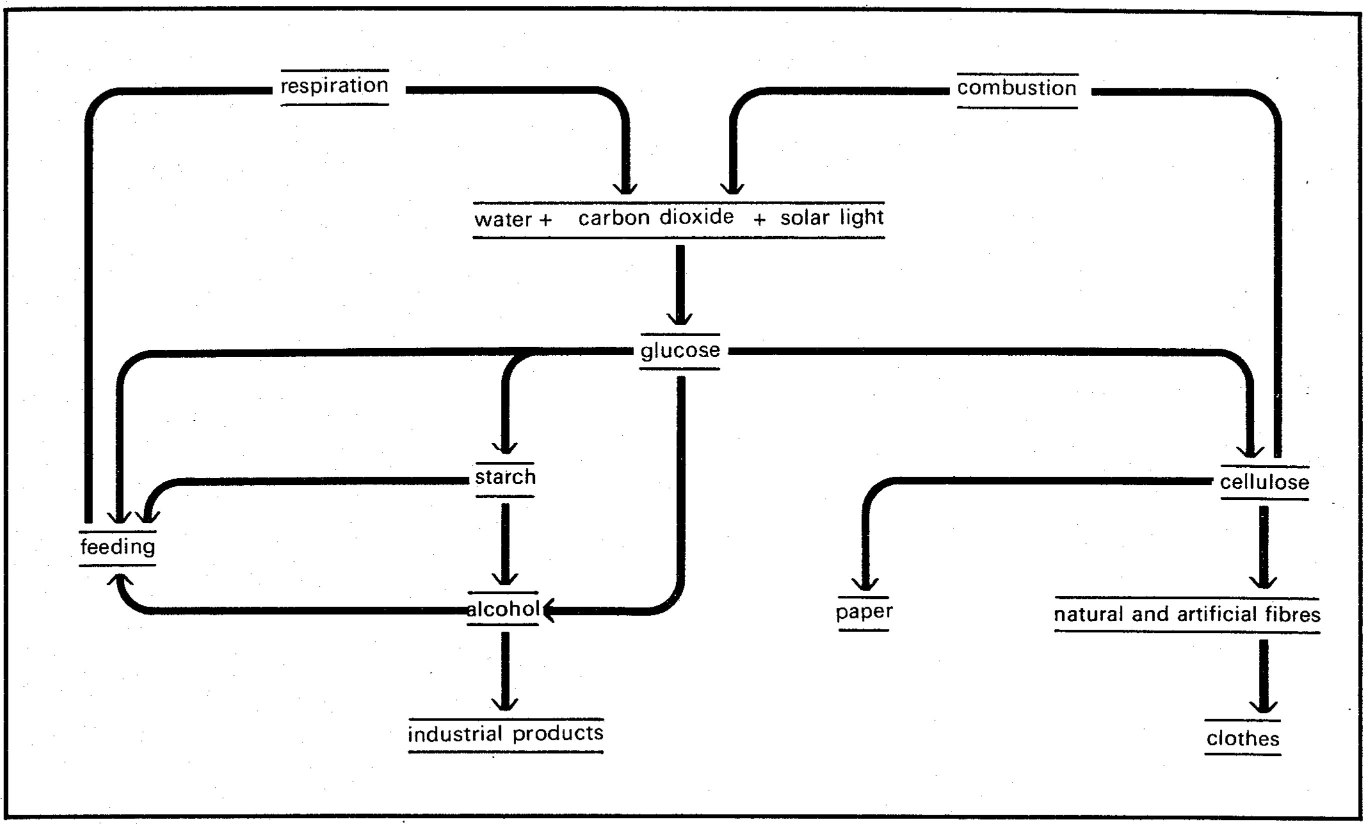


Fig. 7 **A schematic representation of the production and utilization of glucose.**

ation of particular techniques, unnecessary and probably tedious for the reader of this book. In his work he also had to prepare his working instruments, both experimental (like phenylhydrazine) and theoretical. For example, there was an important problem of representing formulae which Fischer resolved with the projection which bears his name (see Fig. 5, p. 22). There was then the problem of attributing one of the two possible configurations, D or L, to each optically active compound. Unfortunately, the rules which relate the sign of rotation to molecular configuration are not well known even now. Compounds with similar structures and identical configurations, that is to say with an identical relative arrangement of the substituents, can have the opposite sense of rotation, and the configuration cannot therefore be uniquely obtained from the sign of rotation. This does not mean, as is often claimed, that there is no relationship between rotation and structure. Such a relationship definitely exists but it is of such a complex nature that it is not easily understood. The attempts being made today, both at the quantum-mechanical level and at the empirical level still have only a limited value and at the beginning of the century the lack of understanding was obviously even greater.

Fischer realized, however, that the problem had two parts. On the one hand there was the problem of attributing a given piece of experimental data (for example, positive optical activity) to one of

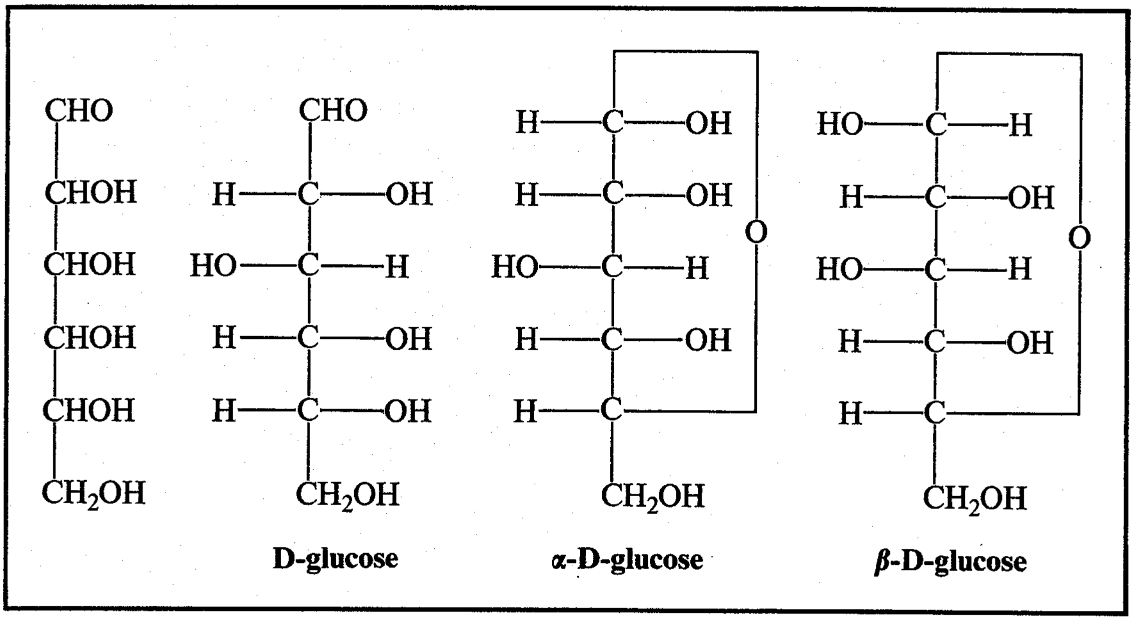


Fig. 8 From left to right: the generic formula of a six-carbon sugar and Fischer projections of D-glucose in the open form and in the two cyclic forms, α-D-glucopyranose and β-D-glucopyranose. In compounds containing several asymmetric atoms each of these is observed as previously described: the horizontal valences are considered to project above the plane of the paper and the vertical ones below.

the two possible configurations, D and L. On the other hand there was the need to establish a series of correlations between compounds with similar structures in such a way as to be able to assign, by comparison, the configuration of a given product (the so-called relative configuration).

The first problem was totally insoluble in his time and was overcome by introducing a conventional nomenclature: a certain spatial formula was arbitrarily assigned to the glyceraldehyde having a positive sign which, in its turn, defined the D configuration (Fig. 9). The second problem was dealt with by assigning the D configuration to all the compounds which can be converted, directly or indirectly, into positive glyceraldehyde without a change in their own configurations. The system of correlations thus obtained is completely self-consistent and of general validity, so much so that its use still continues with only minor modifications in nomenclature (see Appendix II, p. 239).

Turning to the structure of glucose, it must be realized that the linear structure is only an approximation: in reality there is much proof that glucose exists largely in a cyclic form. The aldehydic group is bonded to one of the alcoholic hydroxyls, giving a compound with a cyclic structure in which the ring is formed from five carbon atoms and one oxygen. The simplest compound with this formula is pyran: the name glucopyranose, derived from this, is applied to glucose when it is in the cyclic form.

This cyclization has some important stereochemical consequences. A new asymmetric carbon is formed (Fig. 8) and two different compounds are thus obtained which have the relationship of diastereoimers. They are the α- and β-D-glucopyranose, each having its own physical and chemical characteristics but being easily convertible into the other. Depending on the conditions of crystallization, it is possible to obtain one or other of the two compounds in a solid form. By redissolving each in water it is possible to see that they have a different rotatory power and this varies with temperature until the same value is reached; the same result is obtained by starting either from the α or the β isomer. This phenomenon, called *mutarotation,* is not limited to the case of glucose and shows that in the description of some structures care must be taken not to credit them with a rigidity and stability which they do not possess.

Two contrasting theories of cyclic compounds

A much discussed point in the final decade of the last century concerned the structure and properties of cyclic compounds. It was asked, for example, how to reconcile the tetrahedral arrangement of the carbon valencies with the existence of compounds like cyclopropane in which the angles between the carbon atoms of the ring are about 60°, very far from the theoretical value of about 109°. That the structure of cyclopropane was anomalous was also indicated by its chemical behaviour which is much closer to that of ethylene, an unsaturated compound containing a double bond, than to that of a normal cyclic compound like cyclohexane.

In 1885 Adolph von Baeyer guessed that there must be a relationship between the anomalous valence angle and the enhanced reactivity. He thus formulated a theory of internal strain which for a long time gained acceptance. According to this theory, cyclic compounds must be considered as planar, and the strain, or angular deformation, is considered equal to half the difference between the internal angle of the corresponding regular polygon and the theoretical tetrahedral angle (109° 28′). The greater the strain the less stable should the compound be and the greater its reactivity.

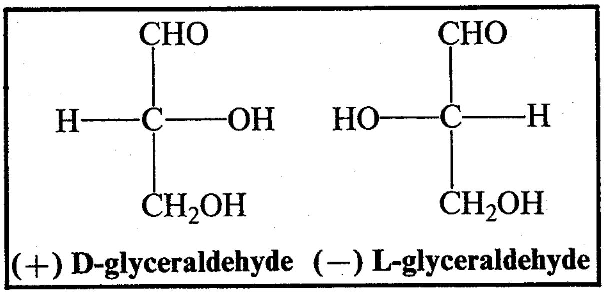


Fig. 9 Fischer projections for D- and L-glyceraldehyde. The assignment of the D formula to the compound with the positive optical rotation was made by Fischer in a purely arbitrary way. But in 1951 this assignment was confirmed experimentally by Bijvoet using the anomalous dispersion of X-rays.

Cyclopentane turns out to be practically free from strain (little more than half a degree); then in a scale of increasing strain follow cyclohexane (about 5°), cycloheptane (more than 9°), cyclobutane, cyclo-octane and so on for other rings (Fig. 10). This scale showed surprising agreement with some experimental facts, for example, the greater ease of formation of five- and six membered rings and their stability. If one then adds that the number of the predictable stereoisomers for each compound in the hypothesis of a planar structure coincides with that found experimentally, it is possible to imagine just how much importance was attached to this theory.

Baeyer's theory is substantially correct for three- and four-membered rings, whose characteristic reactivities can be attributed in good measure to deformation of the valence angles and whose structures are planar (cyclopropane) or little removed from planarity (cyclobutane). For the remainder we can say that the cyclic compounds, although behaving in certain respects as though they were planar, are not in fact planar. The difference in stability between compounds with 7, 8 or 9 atoms, for example, is much less than was predicted and must therefore arise from factors other than strain. However, these facts were not known when, in 1890, Sachse, a then unknown chemist, dared to present a theory for a structure of cyclohexane devoid of strain. Sachse's theory was practically ignored and, as a result, the whole of chemistry suffered a delay of some decades in the development of its systematic interpretation.

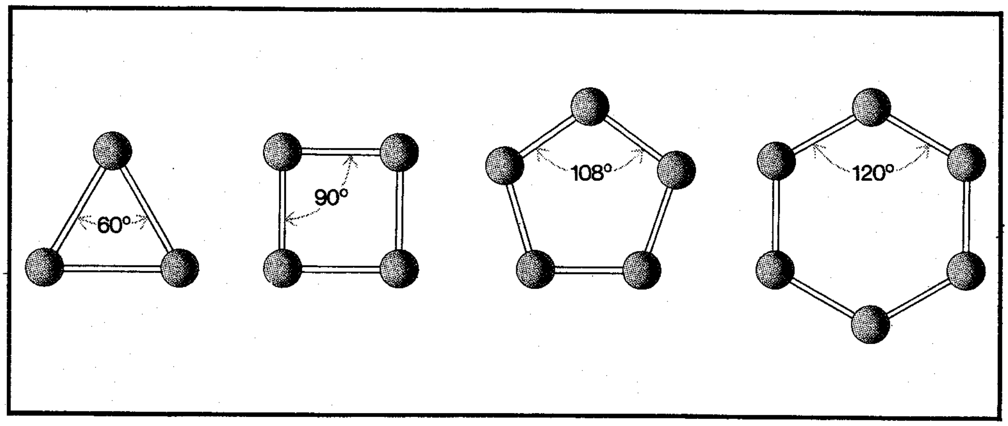


Fig. 10 **Structures of the cyclic hydrocarbons according to Baeyer's theory. This was based on the planarity of the structures and on strain in the valence angles. (The hydrogen atoms are not shown.) Even though it explains some experimental facts, Baeyer's theory is not physically acceptable. Modern investigation has instead confirmed Sachse's hypothesis of the nonplanarity of cyclohexane.**

Linking six carbon atoms with exactly tetrahedral valencies, Sachse saw that two different structures of cyclohexane can exist, one called a 'chair' and the other a 'boat' (Fig. 11). Both structures are non-planar, contrary to one of Baeyer's principles, but they are without angular strain and allow the stability of cyclohexane to be explained.

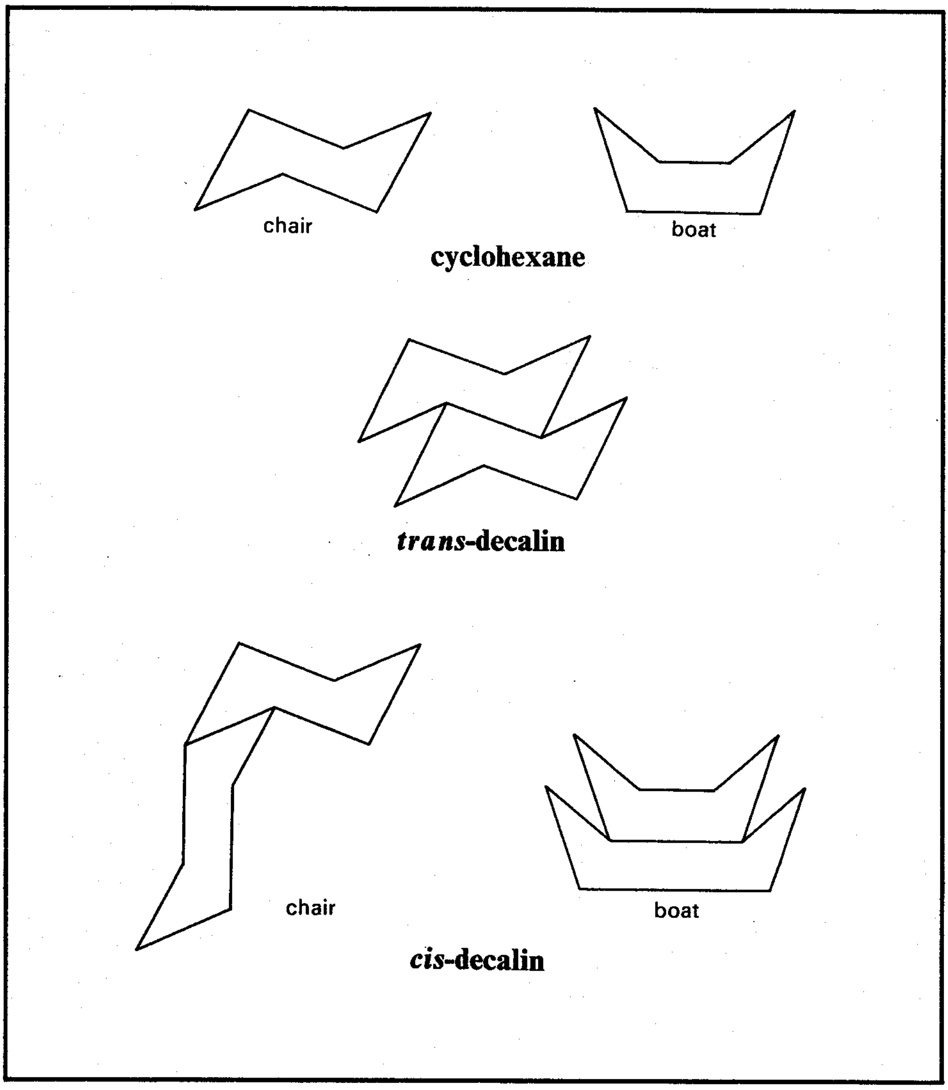
However, if the two structures are considered to be rigid, Sachse's theory would predict the existence of numerous monosubstituted derivatives of cyclohexane. Such derivatives are not found. For example, only one form of methylcyclohexane has ever been observed.

The interpretation put forward for this fact, a rapid exchange between the two different forms,* seemed, at the time, a useless complication. It was better – it was said – to simplify the problem and to describe the system with Baeyer's planar formula than to consider it as the average of two different forms.

It is interesting to note that the criticism explained above, based on the number of isomers, and which blocked Sachse's theory for a long time, later supported the opposite conclusion. About thirty years after its first appearance, the hypothesis of the non-planar forms of cyclohexane was taken up again by the German chemist Mohr and subjected to a decisive test.

By examining models it is possible to see that Sachse's theory allows the existence of two completely hydrogenated derivatives of

Fig. 11 Structures of cyclic hydrocarbons according to Sachse's theory. From above, the chair and boat forms of cyclohexane, the chair form of *trans*-decalin and the chair and boat forms of *cis*-decalin. The most recent investigation has shown that *cis*-decalin exists in the chair form (lower left).



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* This topic will be treated in detail in Chapter III.

naphthalene, *cis*- and *trans*-decahydronaphthalene or decalin. According to the Baeyer theory, only the *cis* form should exist since no model can be constructed of the *trans* form having a planar structure.

The experiment was done by Hückel in 1925 and confirmed Sachse's theory; *cis*- and *trans*-decalin are two different compounds, well-identified and stable and, moreover, the *trans* form is more stable than the *cis* (Fig. 11).

Having established the validity of the non-planar structures of cyclohexane, it still remained to discuss the boat and chair forms. However, this also was a spurious problem. We know today that cyclohexane interconverts from a chair form to a form which is not a boat but another chair. This will be discussed more fully in Chapter III.

Classical and modern stereochemistry

We can now close this historical discussion; we have walked the essential paths of stereochemistry in company with the great protagonists of this adventure: Pasteur, van't Hoff, Fischer and so many others. The inheritance that comes to us from the past is imposing; yet it cannot be denied that it is often a little troublesome. The treatment of cyclic compounds just given provides an example.

The development of scientific knowledge, by its very nature, leads to a very rapid deterioration of theories and schemes of interpretation not only because of new results, which do not always arrive where they are most desired, but also simply from the greater precision of the results themselves. As techniques of investigation evolve, there is an ever greater refinement in experimental work. What could be said yesterday with complete validity must be carefully reviewed today, regarding both the experimental data and their interpretation. In 1935 the purity of a compound or the composition of a mixture could be determined, for example, by measuring the refractive index and the data obtained could be used to develop a hypothesis on a structure or a reaction mechanism. Even in the case where the conclusions obtained were correct, a similar method may no longer be applied. Today this will not content us; more data and wider confirmation are required.

Between 1950 and 1960 the maximum development of infrared spectroscopy occurred. The complete characterization of a new product required the determination of its infrared spectrum. Progress was enormous; the comparison of two products, for example, was simpler and more certain. Instead of one single piece of data, a system of, say, twenty-fifty pieces (the frequency and intensity of absorption bands) was obtained which had to be both self-consistent and consistent within a well-defined series of relationships. But this is still not enough. The infrared spectrum is generally difficult to interpret and it is not always possible to eliminate doubts regarding the purity of a compound. This latter problem was brilliantly overcome by the use of chromatography – particularly gas chromatography – which can detect the presence of impurities, even in the minutest quantities, in a very simple way. At the level of structural interpretation there are the techniques of nuclear magnetic resonance which dominate the field today. Other methods of investigation, such as mass spectroscopy, are becoming more widely used whilst older but largely rejuvenated techniques, such as X-ray and electron diffraction, consolidate their positions.

It is not only because of the larger amount of data and the greater precision of these techniques that the situation has altered. Knowledge of an unforeseen type has emerged and totally unexpected phenomena have been observed. All this, as well as a greater feeling for the formal and mathematical aspects of the problem, is at the base of modern stereochemistry. But before passing to new topics, we should like to draw attention to a result which in a certain sense concludes an era, even though it was obtained by using very refined modern techniques.

In talking about the configuration of glyceraldehyde, we said that Fischer arbitrarily assigned the D configuration to the positive optical antipode (see Fig. 9). Fischer had nothing which would help him in his choice or verify the convention he chose. There was no experiment available to him at that time which could do that. It was necessary to imagine a new type of experiment to relate what we today call the chirality (i.e., being dextro or laevo) of a molecule with the everyday perception of right and left.

It is to the credit of the Dutchman Bijvoet that this relationship has been known since 1951. Using the anomalous dispersion of X-rays he ascertained that positive tartaric acid has the configuration illustrated in Fig. 6. As the relationship between the configuration of (+)-tartaric acid and that of (+)-glyceraldehyde had already been found chemically, it was possible to establish that this latter really had the D configuration.

Thus Fischer, by luck, was correct in his choice.

II

Atoms and molecules

Anyone who reads the papers or watches television today knows, to some extent at least, the meaning of words like atom, molecule, electron and so on. The importance of the discoveries of recent years and the attention given to them hardly permits complete ignorance in these matters. In the scientific world, however, atoms have been discussed for more than a century and a half and it is a great achievement of nineteenth century chemistry to have introduced and developed the atomic theory of matter, a theory which is only in superficial respects and by name related to the ancient theory of Leucippus and Democritus.

The matter which we usually touch and observe is, in general, a mixture which is divided, at the chemical level, into elements and compounds. The first consists of atoms all identical with each other; the second of atoms of different types. The smallest aggregate of atoms is called a molecule.

Now, whilst there is an extremely large number of different types of molecules (or chemical compounds) the atomic species (or elements) are relatively few, there being about one hundred. Atoms have the capacity of bonding to each other according to well-defined laws; but the nature of the chemical bond (or of valency) has given rise to one of the most interesting and profound debates of modern science.

Valency was often represented symbolically by a given number of hooks, by means of which the atoms could join with the hooks of other atoms. Stoichiometric or quantitative relationships existing in different compounds can be explained in this way; but it does not shed any light on the forces holding atoms together or on the reasons why molecules possess particular properties. The first valid replies to these problems were given about fifty years ago. But the theories which have since been developed depend very much on a mathematical basis which is not very suitable for a simple treatment; any such simplification inevitably distorts the theories. Atomic and subatomic phenomena do not lend themselves readily to visualization in terms of normal language, because they are based on laws that do not always find their correspondence in the macroscopic world, and the models proposed for them are quite often very inadequate.

Our description will be very approximate; it will obviously neither satisfy the atomic physicist nor the quantum-mechanical physical chemist. We propose only to give an idea of the actual problem and to search for a simple explanation of certain phenomena and of molecular structures.

From the periodic system of the elements to the Bohr atom

One of the landmarks in the development of the modern theory of valency is the periodic system of the elements, proposed by Mendeleev in 1869. The ordering of the elements according to their relative weights (i.e., atomic weights) gave rise to some very characteristic progressions: ignoring the two lightest elements, hydrogen and helium, the sequence (lithium, beryllium, boron, carbon, nitrogen, oxygen, fluorine and neon) constitutes a series in which the properties vary in a drastic but continuously progressive way. For example, the number of hydrogen atoms with which each of these can be bonded goes from one (lithium) to a maximum of four (carbon) and returns to one (fluorine) and finally zero (neon). What we today call electronegativity, which one hundred years ago was expressed in terms of metallic or non-metallic character, also varies in a continuous way and increases regularly from lithium to fluorine.

Sodium, the element whose atomic weight is next above that of neon, has properties very similar to those of lithium; in the same way, magnesium is closely related to beryllium. These relationships continue with aluminium associated with boron, silicon with carbon, phosphorus with nitrogen, sulphur with oxygen, chlorine with fluorine and argon with neon. After these two periods of eight elements, another two more complex periods of 18 elements can be recognized and finally a very large period consisting of 32 elements. The heavier elements, which occupy the positions above the 86 now mentioned, form part of a further period which is largely incomplete (Fig. 12).

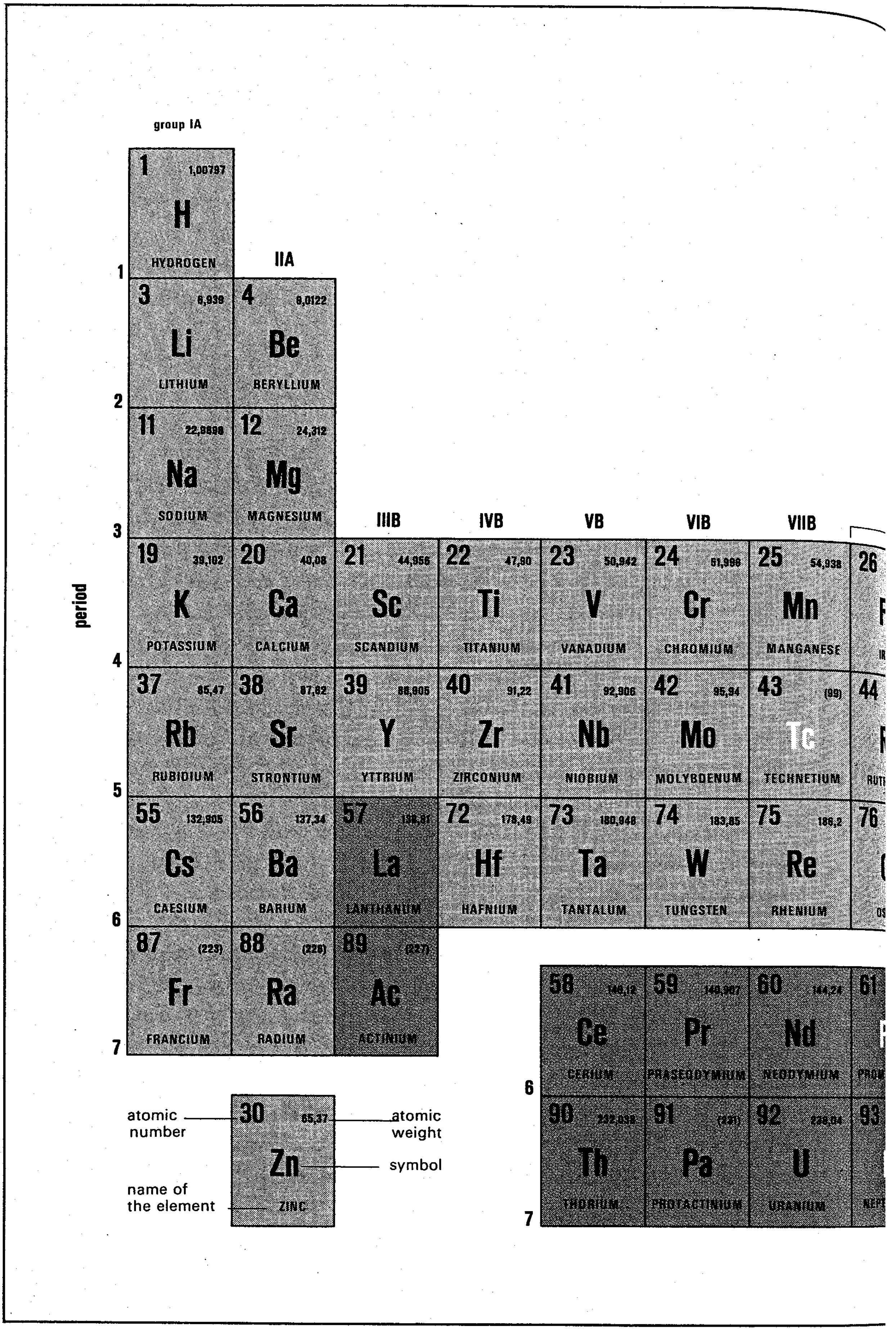
Mendeleev's genius can be better appreciated if one realizes that in his time many elements were still unknown. But not only did he leave the respective spaces empty but even managed to predict some of the properties of the unknown elements. The so-called transition elements and the lanthanides found a place in the classification, although with more difficulty.

The periodic system of the elements has undergone some modifications, but it has remained substantially unaltered right up to the present time. We shall see later how it has acquired a fundamental significance in the modern interpretation of atomic structure. One of the most important observations concerns the atomic number or, rather, the number of the position that an element occupies in the periodic table. The X-ray emission spectra studied by Moseley have given this number a physical significance of enormous importance. The atomic number is equal both to the number of protons and to the number of electrons in the atom. Apart from some small irregularities the two arrangements, based respectively on the atomic weight and on the atomic number, coincide but the second is endowed with a more general validity and has a fundamental physical significance.

The discovery of radioactivity brought other contributions to the knowledge of atomic structure. The atom was no longer an indivisible particle but was found to be formed from a nucleus, containing almost all the mass and having a positive electrical charge, surrounded by a cloud of negatively-charged electrons. It is of no interest for our purposes to specify further the structure of the atomic nucleus (the dominion of nuclear physics) because the experimental and theoretical evidence commonly accepted today places the origin of valency and chemical phenomena in the electronic sphere. We shall confine our attention to this only from now on.

A well-known model represents the atom as a planetary system. The nucleus, like the sun, is at the centre and the electrons, like the planets, revolve around it in circular or elliptical orbits. However, according to the principles of classical mechanics, the electrons, by rotating in their orbits, should radiate energy and the radius of the orbits should continually decrease until finally the electrons fall into the nucleus, as an artificial satellite, at the end of its life, falls into the earth's atmosphere. These deductions, however, are contrary to the experimental facts.

The solution of this problem came from the study of atomic spectra. Many elements, when heated to a high temperature, produce a characteristic light, the spectrum of which shows well-defined lines, or colours. These well-defined lines indicate that emission, or absorption, of luminous energy is taking place at specific values and not across the whole range. Meanwhile, Max Planck had postulated the existence of quanta as indivisible units of energy and had written the famous equation $\Delta E = h\nu$ which related the energy of radiation to its frequency ν through the constant h, called Planck's constant. On the basis of this theory, the presence of lines in the spectrum can be interpreted as the result of an exchange



period	group IA	IIA	IIIB	IVB	VB	VIB	VIIB
1	1 1,00797 H HYDROGEN						
2	3 6,939 Li LITHIUM	4 9,0122 Be BERYLLIUM					
3	11 22,9898 Na SODIUM	12 24,312 Mg MAGNESIUM					
4	19 39,102 K POTASSIUM	20 40,08 Ca CALCIUM	21 44,956 Sc SCANDIUM	22 47,90 Ti TITANIUM	23 50,942 V VANADIUM	24 51,996 Cr CHROMIUM	25 54,938 Mn MANGANESE
5	37 85,47 Rb RUBIDIUM	38 87,62 Sr STRONTIUM	39 88,905 Y YTTRIUM	40 91,22 Zr ZIRCONIUM	41 92,906 Nb NIOBIUM	42 95,94 Mo MOLYBDENUM	43 (99) Tc TECHNETIUM
6	55 132,905 Cs CAESIUM	56 137,34 Ba BARIUM	57 138,91 La LANTHANUM	72 178,49 Hf HAFNIUM	73 180,948 Ta TANTALUM	74 183,85 W TUNGSTEN	75 186,2 Re RHENIUM
7	87 (223) Fr FRANCIUM	88 (226) Ra RADIUM	89 (227) Ac ACTINIUM				

period			
6	58 140,12 Ce CERIUM	59 140,907 Pr PRASEODYMIUM	60 144,24 Nd NEODYMIUM
7	90 232,038 Th THORIUM	91 (231) Pa PROTACTINIUM	92 238,03 U URANIUM

atomic number — 30
atomic weight — 65,37
symbol — Zn
name of the element — ZINC

Fig. 12 A modern representation of the periodic system of the elements. The horizontal rows define the periods and the vertical rows the groups. The groups lettered A comprise the normal elements, from the alkali metals to the halogens. The noble gases are the group on the right without a number. The elements

	IB	IIB	IIIA	IVA	VA	VIA	VIIA	inert gases
								2 4,0026 He HELIUM
			5 10,811 B BORON	6 12,0111 C CARBON	7 14,0067 N NITROGEN	8 15,9994 O OXYGEN	9 18,9984 F FLUORINE	10 20,183 Ne NEON
			13 26,9815 Al ALUMINIUM	14 28,086 Si SILICON	15 30,9738 P PHOSPHORUS	16 32,064 S SULPHUR	17 35,453 Cl CHLORINE	18 39,948 Ar ARGON
28 58,71 Ni NICKEL	29 63,54 Cu COPPER	30 65,37 Zn ZINC	31 69,72 Ga GALLIUM	32 72,59 Ge GERMANIUM	33 74,922 As ARSENIC	34 78,96 Se SELENIUM	35 79,909 Br BROMINE	36 83,80 Kr KRYPTON
46 106,4 Pd PALLADIUM	47 107,870 Ag SILVER	48 112,40 Cd CADMIUM	49 114,82 In INDIUM	50 118,69 Sn TIN	51 121,75 Sb ANTIMONY	52 127,60 Te TELLURIUM	53 126,904 I IODINE	54 131,30 Xe XENON
78 195,09 Pt PLATINUM	79 196,967 Au GOLD	80 200,59 Hg MERCURY	81 204,37 Tl THALLIUM	82 207,19 Pb LEAD	83 208,980 Bi BISMUTH	84 (210) Po POLONIUM	85 (210) At ASTATINE	86 (222) Rn RADON

63 151,96 Eu EUROPIUM	64 157,25 Gd GADOLINIUM	65 158,924 Tb TERBIUM	66 162,50 Dy DYSPROSIUM	67 164,930 Ho HOLMIUM	68 167,26 Er ERBIUM	69 168,934 Tm THULIUM	70 173,04 Yb YTTERBIUM	71 174,97 Lu LUTETIUM
95 (243) Am AMERICIUM	96 (247) Cm CURIUM	97 (247) Bk BERKELIUM	98 (251) Cf CALIFORNIUM	99 (254) Es EINSTEINIUM	100 (253) Fm FERMIUM	101 (256) Md MENDELEVIUM	102 (254) No NOBELIUM	103 (257) Lr LAWRENCIUM

21–30, 39–48, 57–80 and from 89 onwards are called the transition elements. The elements 57–71 (the lanthanides or rare earths) occupy a special place in the periodic system as do the elements beyond 88, the actinides. The majority of the latter are artificial elements, obtained by means of nuclear reactions.

of *quantized* energy. The atom or electron can only accomplish certain transitions (changes from one energy level to another); in a transition it emits or absorbs finite quantities of energy which correspond to those of the emitted or absorbed radiations.

In 1913 Niels Bohr proposed an atomic model based on the above considerations – and others. In Bohr's model the very small central nucleus is positively charged, possesses a number of protons equal to the atomic number, and a weight roughly equal to the sum of the protons and neutrons (particles with almost the same mass as a proton but of zero charge). The electrons, equal in number to the protons, move in external orbits, neither absorbing nor emitting energy. Each orbit is quantized in that it is defined by an integral number 1, 2, 3, etc. called the *principal quantum number* and the energy possessed by an electron in a given orbit is proportional to the reciprocal of the square of the corresponding quantum number. The passage of an electron from one orbit to another (the excitation or de-excitation of an electron) causes a change of energy which corresponds to a well defined frequency in the spectrum. In this way Bohr succeeded in calculating a theoretical spectrum of hydrogen which is in good agreement with that obtained experimentally.

The transitions in heavier atoms and the attempt to interpret certain spectroscopic phenomena produced by magnetic fields brought to light several shortcomings in the Bohr model. It has been modified by the introduction of three further *quantum numbers: azimuthal, magnetic* and *spin.* With four quantum numbers it is finally possible to interpret the spectroscopic phenomena of the various elements in terms of the Bohr model. However, a discussion of valency requires a further insight into the fundamental behaviour of matter and this will now be dealt with.

The electron: wave or particle?

One of the most fascinating problems of classical physics concerned the nature of light. Is light composed of particles hurled at fantastic velocities against the illuminated object or is it a propagation in space (or as it was once called, the ether) of waves similar to those of the sea?

The majority of optical phenomena can be explained in terms of both theories. However, some experiments seemed explicable only by a wave theory. During the nineteenth century the wave theory of light progressively gained the upper hand and Maxwell's equations gave it a mathematical support of rare elegance. At the end of the century, however, the discovery that energy is not transmitted in continuous quantities but as finite and discontinuous entities (Planck's quanta) gave new vigour to the alternative corpuscular theory. It is believed today that the corpuscular and wave interpretations are two views of the same reality and that depending on convenience one can change from one approach to the other without involving a violation of principle.

This discussion may seem very far from our basic problem and indeed it would be pointless to mention it if it had not once more upset the model that science had built for the atom. In 1924 Louis de Broglie had a really revolutionary idea: if waves or particles are two aspects – two equivalent descriptions – of light and optical phenomena, why should it not be possible to apply a similar dual interpretation to matter, and thus to the atom and the electron? This was not just an esoteric theory: today, electron microscopes and electron diffractometers are in common use and by means of them the wave properties of the electrons are employed in chemical and biological studies.

But beyond the experimental level, de Broglie's ideas were of decisive importance for the study of atomic structure. If the atom and electron can be interpreted in terms of waves, it should be possible to apply to them the standard mathematical methods of treating waves. The Austrian, Erwin Schrödinger, today considered the father of wave or quantum mechanics, developed this approach.

Let us try to give an idea of this approach with a musical comparison. A violin string stroked by the bow begins to vibrate, emitting a sound which corresponds to a definite note, for example, *C natural.* But what makes the sound of the violin particularly pleasing, and different from the sound of the oboe or the flute? It is the timbre, or the resonant sensation which depends on the quality of the vibration. This is not, in fact, a simple oscillation that can be described sinusoidally but is a combination of the fundamental note with its harmonics; apart from the first, it contains, with greater or lesser intensity, vibrations corresponding to *C natural* and *G natural* of the next octave and so on. The harmonics have frequencies which are exact multiples of the fundamental note, i.e., doubled, tripled, etc. In other words, the resolution of the wave equation for a violin string has a physical significance only for integral multiples of a certain quantity (Fig. 13).

If in place of a string we cause a two-dimensional lamina to vibrate, e.g., the drum or the cymbals of an orchestra, we must write a two-dimensional wave equation. By suitable means it is possible for the vibrational mode, i.e., the different solutions of the wave equation of a lamina, to be made visible (Fig. 14).

The Schrödinger equation which describes the movement of the electrons of the hydrogen atom is formally analogous to the acoustic equation just described and, like it, has only certain well-defined solutions. These can be obtained by introducing into the values for the energy a series of integral numbers, associated with each other through precise relationships. Here arising in wave terms and from a purely mathematical treatment are those numerical quantities which were necessary for explaining the spectroscopic phenomena. These still have the names of the old Bohr theory: n is the principal quantum number and can have values 1, 2, 3 . . . .; l is the azimuthal quantum number, taking the values 0, 1, 2 . . . up to $n-1$; m is the magnetic quantum number, whose values are $m = 0, \pm 1, \pm 2, \pm 3 \ldots \pm l$. Finally, there is the spin quantum number m_S which can have only the values $+\frac{1}{2}$ and $-\frac{1}{2}$ and which was introduced into the quantum-mechanical theory at a later stage, although it plays a decisive part in the problem which interests us.

Every solution of the Schrödinger wave equation characterized by the first three quantum numbers (n, l, and m) is called an orbital. In particular, the solution that is obtained by putting $n = 1$, $l = 0$ and $m = 0$ represents the most stable orbital of the hydrogen atom. The calculation shows that there is an exact correspondence between this orbital and the orbit of the Bohr atom; but the quantum mechanical treatment also shows itself to be in complete agreement with another postulate of atomic physics, Heisenberg's uncertainty principle.

Returning to our musical example, we know that the violin string emits a sound the strength of which depends on the force with which the string is made to vibrate. The intensity of the sound depends on the amplitude of the vibration and, more precisely, is proportional

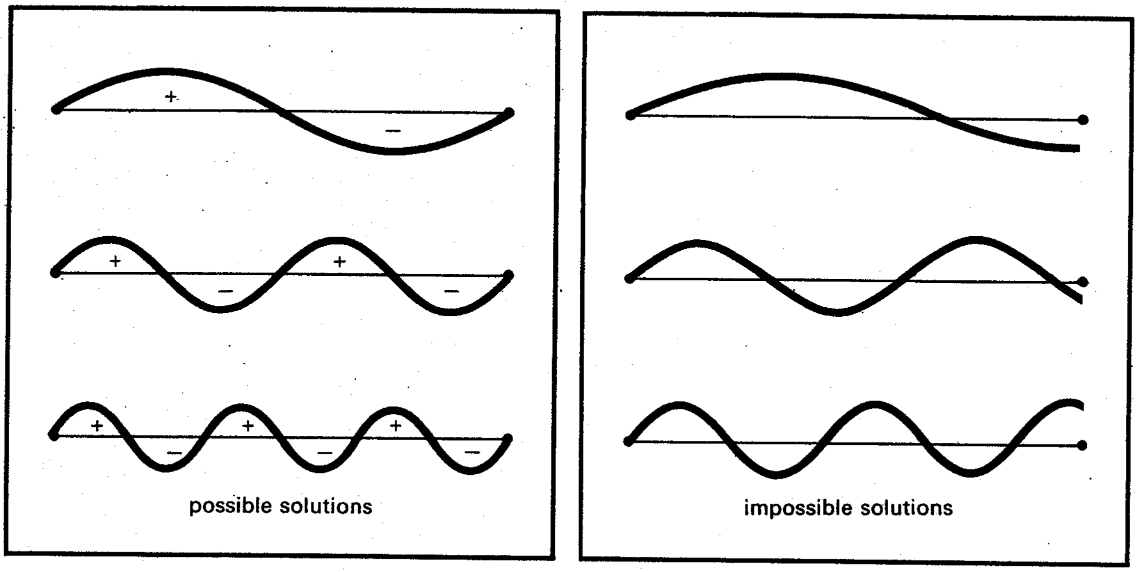


Fig. 13 The wavelength of the vibrations of a violin string is a sub-multiple of the length of the string (one, a half, a third, a quarter, etc.). Other frequencies are impossible because nodes would not occur at the end of the string. (Nodes are the points at which the amplitude of the vibrations is zero.) At every point it is possible to define the sign, positive or negative, of the vibration.

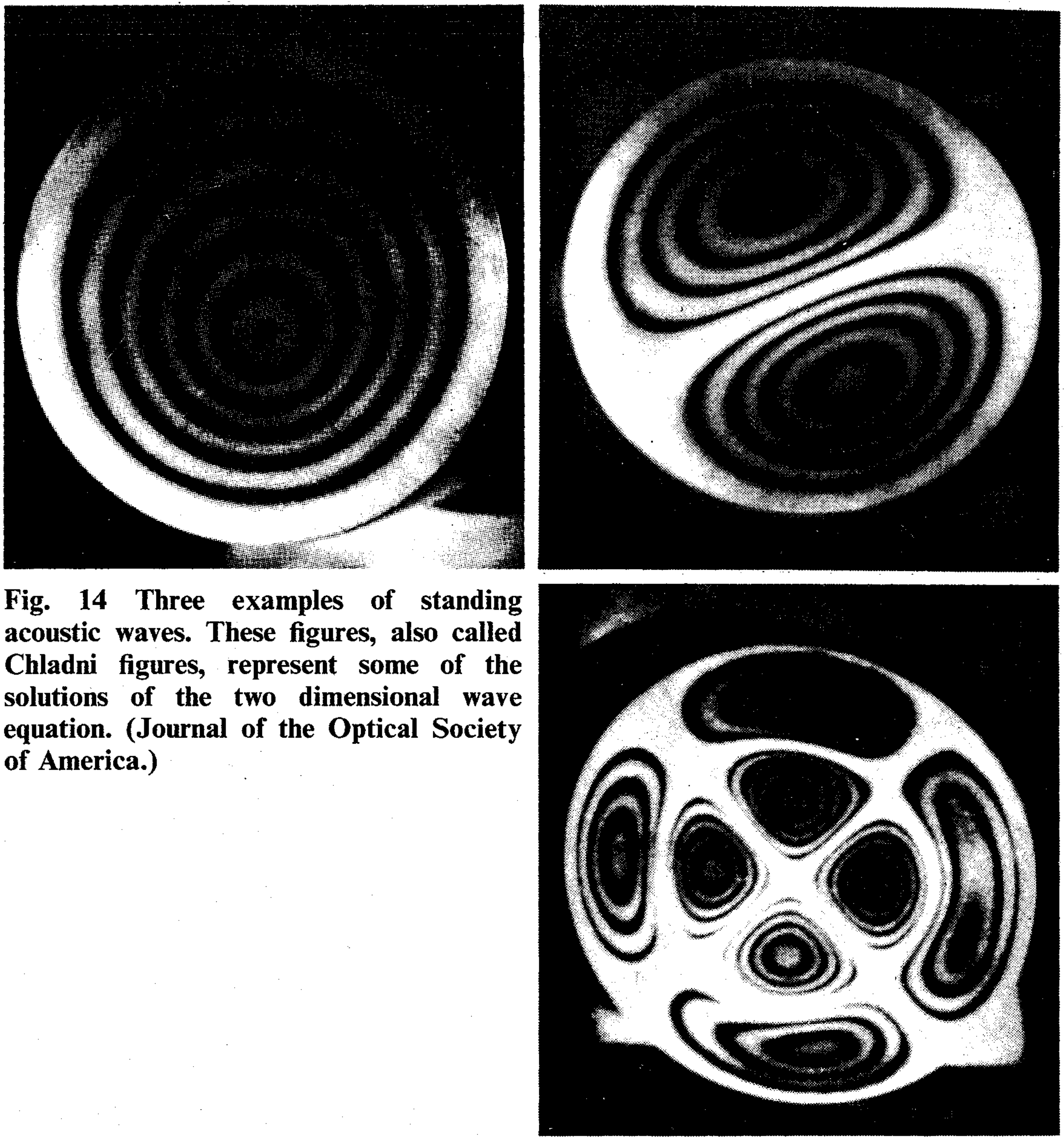


Fig. 14 Three examples of standing acoustic waves. These figures, also called Chladni figures, represent some of the solutions of the two dimensional wave equation. (Journal of the Optical Society of America.)

to the square of the amplitude. This relationship is valid for optical phenomena also, but in this case, on passing from the wave to the corpuscular theory, the concept of intensity must be expressed in terms of particle density. A light ray is greater in intensity the greater the amplitude of vibration of the electromagnetic field or, in an equivalent way, the greater the number of corpuscles (photons) which strike a given target. Let us apply these considerations to our case.

The orbital is a mathematical expression giving the solutions of the wave equation of the electron and is normally symbolized by the Greek letter ψ: the value of ψ (or, better, of ψ^2) at a certain point in space is related to the density of electronic charge at that point. Charge density is a typically statistical expression and refers to a very large number of events. Since a single object, a single electron, is to be observed the charge density must be replaced by a more appropriate expression, one involving probability.

ψ^2 can be defined as the probability of finding an electron in a certain point of space. The value of this probability and the zone of space in which the probability is highest varies according to the quantum numbers, as we shall soon see.

For the moment we are concerned to make clear the probability character of the theory. The Bohr orbit and the Schrödinger orbital display many analogies but while in the first description the electron must definitely be found on the orbit in the second the electron has a finite probability of existence away from the orbit (Fig. 15). More exactly, we cannot determine in a precise way the position of the electron within the orbital and we can only give a description of it in terms of probability. In this sense the quantum-mechanical treatment is in agreement with Heisenberg's principle which establishes intrinsic limits to our capacity for observing electronic phenomena.

Orbitals and the system of elements

With reluctance, we find it necessary to introduce further technical notation. The use of a precise terminology will allow us to be quicker without, we hope, sacrificing comprehensibility.

The nomenclature in use for the orbitals consists of a number and a letter which depend on the values of the quantum numbers n and l: the number corresponds to the value n (1, 2, 3, etc.), while the letter refers to the value of l: s for $l = 0$, p for $l = 1$, d for $l = 2$ and f for $l = 3$. A 1s orbital thus has $n = 1$ and $l = 0$. From the selection rules given above there can only be one s orbital (m can have only a single value: 0), three p orbitals ($m = -1, 0, +1$), five d ($m = -2$,

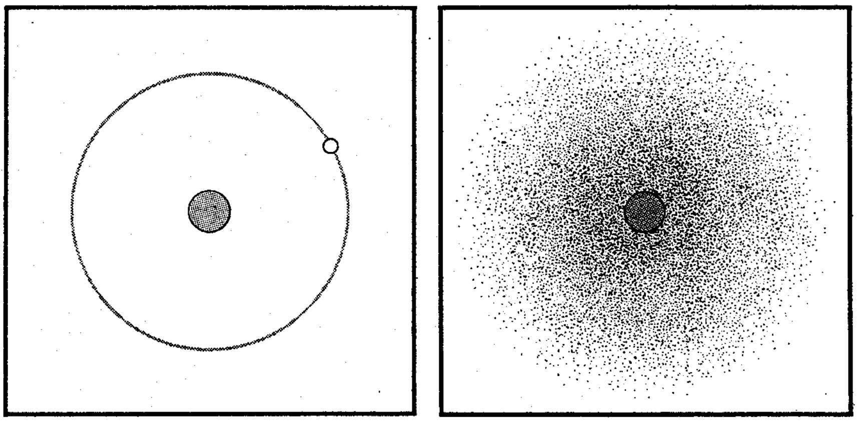


Fig. 15 According to Bohr's theory the electron of the hydrogen atom in the ground state revolves around the nucleus with a fixed radius, equal to 0·053 nm. According to quantum-mechanical theory it is possible to speak only about the probability of finding the electron at a given distance from the nucleus. The probability is at a maximum on a sphere of radius equal to that of the Bohr orbit but also has finite values at greater and lesser distances from the nucleus.

$-1, 0+1, +2$) and seven f ($m = -3, -2, -1, 0, +1, +2, +3$). For $n = 1$ only a single orbital is thus possible, the 1*s*; for $n = 2$ there are four, a 2*s* and three 2*p*; for n = 3 there are nine (a 3*s*, three 3*p* and five 3*d*); for n = 4 there are sixteen (a 4*s*, three 4*p*, five 4*d* and seven 4*f*) (Table II).

The *s* orbitals have a spherical shape and thus the corresponding electronic clouds will also be spherical, the probability of finding an electron diminishing as the distance from the nucleus increases. To give a visual representation of the shape and dimensions of such a distribution, an appropriate surface is used which encloses the zone of space containing almost all (90 or 95 per cent) of the total charge (Fig. 16).

Table II. Relationship between quantum number and type of orbital

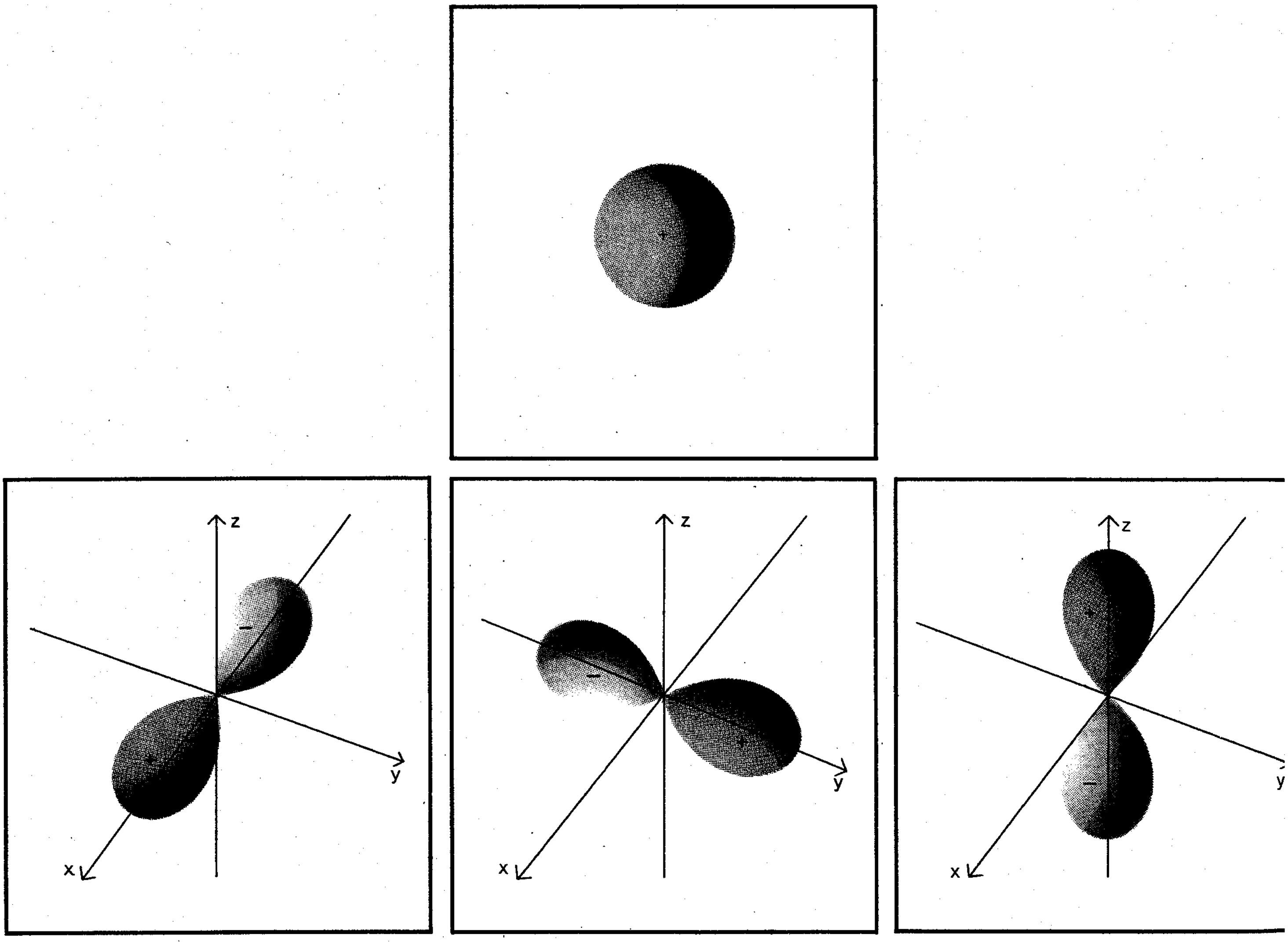
Quantum number			Orbital		
principal	azimuthal	magnetic	name	number	
1	0	0	1*s*	1	
2	0	0	2*s*	1	4
2	1	$-1, 0, +1$	2*p*	3	
3	0	0	3*s*	1	9
3	1	$-1, 0, +1$	3*p*	3	
3	2	$-2, -1, 0, +1, +2$	3*d*	5	
4	0	0	4*s*	1	16
4	1	$-1, 0, +1$	4*p*	3	
4	2	$-2, -1, 0, +1, +2$	4*d*	5	
4	3	$-3, -2, -1, 0, +1, +2, +3$	4*f*	7	

Each *p* orbital consists of two lobes touching each other at the atomic nucleus and the orbitals themselves are orientated along three orthogonal axes; depending on the direction of orientation they are called p_x, p_y and p_z. The *d* orbitals have a more complex shape (Fig. 16). It is interesting to relate these orbitals to the Chladni figures for acoustic vibrations (see Fig. 14).

As we have already observed for linear waves (see Fig. 13) the wave function ψ can assume positive and negative values and can also have a change of sign within a single orbital. The *s* orbitals have a positive sign in every point, while the lobes of the *p* and *d* orbitals have alternatively positive and negative signs (Fig. 16).

There can only be a maximum of two electrons in each orbital. This is a consequence of another physical principle: Pauli's exclusion principle. Its general statement is the following: there cannot exist in an atom (or in an interacting system) two electrons with the same four quantum numbers. Since an orbital is defined by three quantum numbers there remains only one alternative, that the electrons have a spin $+\frac{1}{2}$ or $-\frac{1}{2}$. Consequently the numbers for the orbitals existing for each value of *n*, which we have already seen to be 1, 4, 9 and 16, must be doubled to give the number of electrons which can occupy these orbitals; 2, 8, 18, 32. It will be recalled that these are the numbers which distinguish repetitions in the periodic system of the elements (see p. 36). We have perhaps found the key to its interpretation.

Before continuing, it is necessary to define the energetic aspect of the problem more accurately. The energy of a given orbital is a function firstly of the quantum number *n* and secondly of *l*, and the energy difference between successive levels diminishes as *n* grows. Moreover, there is no clear separation between the orbitals of the successive shells, that is to say of those distinguished by a different quantum number *n*. A 3*d* orbital has an energy very close to that



of the $4s$ and a $4f$ to that of the $6s$. The energy levels of different orbitals are indicated in Fig. 17.

We have thus prepared a sort of bookcase, with as many cells as there are orbitals, in which we can place the electrons of different elements. If we begin to fill it by starting at the bottom, i.e., by putting in the electrons most strongly attracted by the nucleus, we can confirm that the experimental order observed by Mendeleev has its roots in the arrangement of the electrons around the nucleus, in the so-called electronic configuration of the atom.

Hydrogen has a single electron, for which there are no problems; in the ground state (lowest energy) it is placed in the $1s$ orbital. Helium has two electrons and to conform with the Pauli principle we must put them in the same orbital but with antiparallel spins, one having spin $\frac{1}{2}$ and the other spin $-\frac{1}{2}$. Lithium, with three electrons, has the electronic configuration $1s^2$, $2s^1$ (which is read as one-ess, two; two-ess, one, and signifies two electrons in the $1s$ orbital and one electron in the $2s$ orbital); beryllium $1s^2$, $2s^2$; boron $1s^2$, $2s^2$, $2p^1$; carbon $1s^2$, $2s^2$, $2p^2$ and so on to neon $1s^2$, $2s^2$, $2p^6$. Sodium has

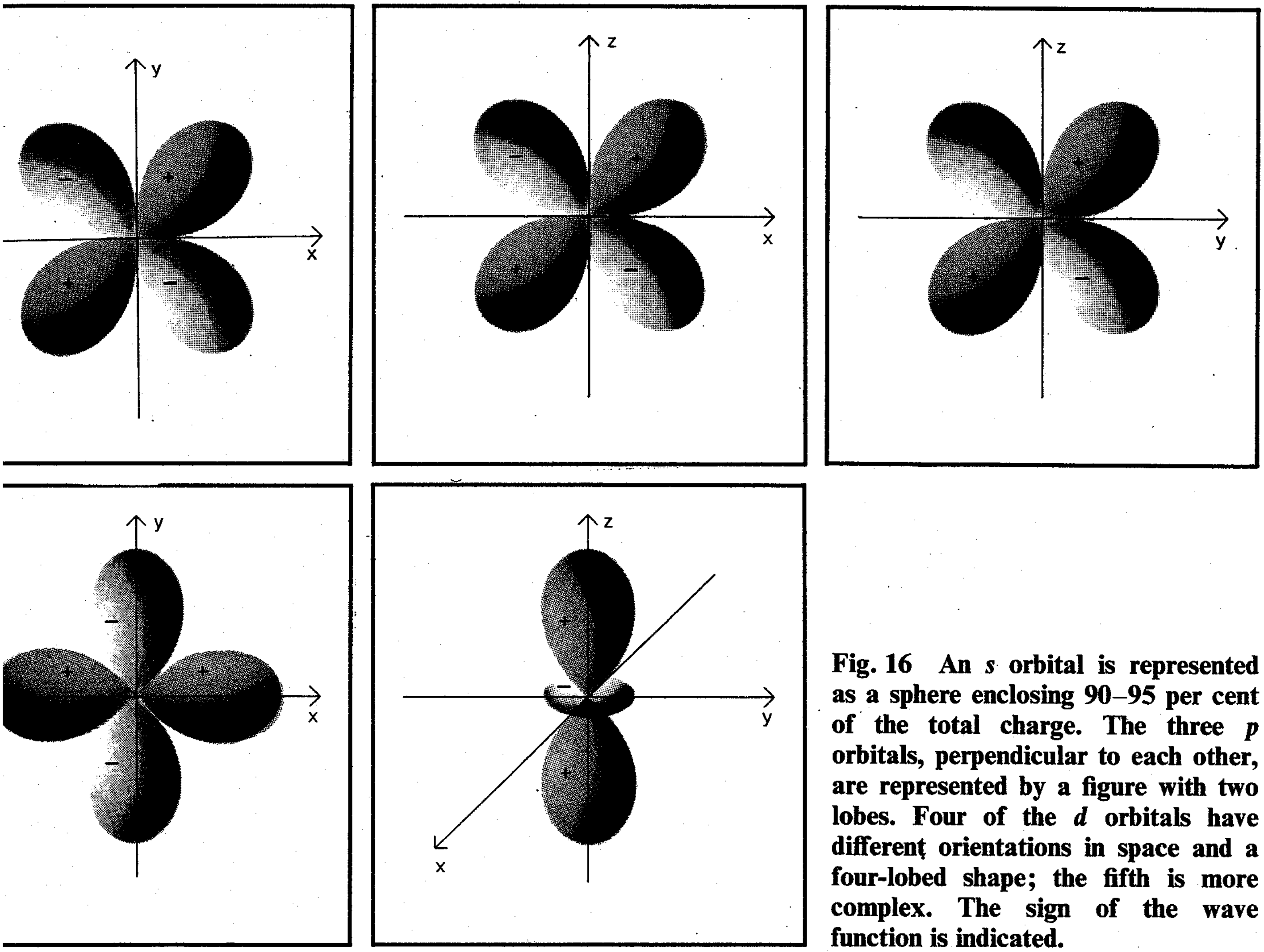


Fig. 16 An s orbital is represented as a sphere enclosing 90–95 per cent of the total charge. The three p orbitals, perpendicular to each other, are represented by a figure with two lobes. Four of the d orbitals have different orientations in space and a four-lobed shape; the fifth is more complex. The sign of the wave function is indicated.

the electronic configuration Ne, $3s^1$ (i.e., that of neon with one electron more), similar to that of lithium (He, $2s^1$). A ready explanation for the notable similarity in chemical behaviour between these two is thus obtained.

We can state a general rule: the chemical properties of an element essentially depend on its outer electronic configuration, that is to say upon the number of electrons present in the so-called valence shell. Thus we have the series of the noble gases, elements endowed with exceptional stability – neon, argon, krypton, xenon and radon – with the external electronic configuration ns^2, np^6 (the first of the noble gases, helium, has the configuration $1s^2$, because no p orbital exists for the shell 1); another series of alkali metals – lithium, sodium, potassium, rubidium, caesium – having the configuration ns^1, one electron more than the nearest noble gas; and another of halogens – fluorine, chlorine, bromine and iodine – with the configuration ns^2, np^5.

The transition elements – for example, scandium, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper and zinc – are characterized by the progressive filling of the *d* orbitals (up to a maximum of 10 electrons) and the lanthanides by the filling of the *f* orbitals (up to 14 electrons).

The electronic configuration of the elements shown in Table III can be usefully compared with the periodic system already illustrated (see Fig. 12, p. 36). The correspondence between the chemical properties and the electronic structure is perfect and complete. To have found this relationship constitutes one of the most important results in the history of modern science.

Chemical valency as an electronic phenomenon

Before atomic structure was expressed in the terms indicated above, chemists had clearly understood the electrical (or electronic) nature of the chemical bond. That water could be dissociated into its components, hydrogen and oxygen, by the action of a current and that electricity could be produced directly from a cell by a chemical reaction were very clear indications of this. Based on the non-quantized atomic model, the planetary system formed by the nucleus and electrons, a satisfactory treatment for many aspects of the chemical bond was developed in the first decades of the century, a treatment which culminated in the theories of Lewis and Langmuir.

Above all, the existence of two fundamental types of chemical bond was made quite clear. These are the ionic bond and the covalent bond. The former is present in many salts in the solid state, ordinary table salt NaCl being a typical example.

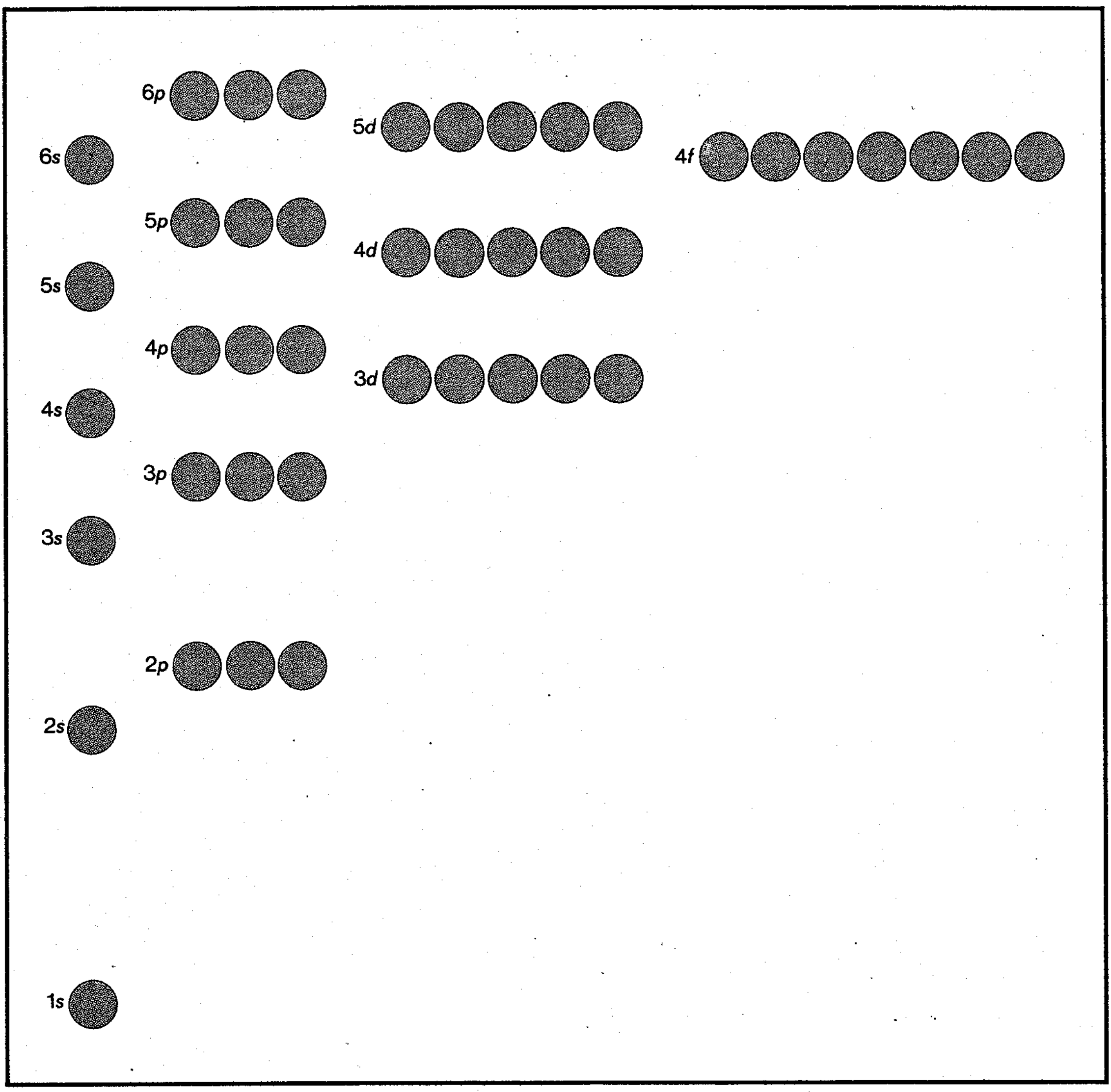


Fig. 17 **Representations of approximate energy levels for the different atomic orbitals. From the bottom upwards one passes from the most stable (ls) orbital to those with higher energies. The separation between the levels of the different orbitals diminishes as the energy increases.**

In the periodic table, chlorine and sodium are found respectively immediately before and immediately after the noble gases, elements which we know to be endowed with a particularly stable electronic structure. It seems very plausible, therefore, that a process should take place in which the sodium loses an electron which the chlorine atom gains. In such a case both elements finish with the structure of a noble gas, but there is no longer a balance between the positive charge of the nucleus and the negative one of the electrons. The sodium atom emerges with a positive charge, that is to say it is transformed into a positive ion or cation (Na^+), while the chlorine becomes a negative ion or anion (Cl^-).

In the crystalline state the atoms attract each other electrostatically because of their opposite charges and form a very stable system. In the presence of water, however, salt dissolves and the two ions are free to move throughout the solution. This loosening and

Table III. Electron configurations of the elements*

element	atomic number	number of the electrons in each sub-shell																			
		1*s*	2*s*	2*p*	3*s*	3*p*	3*d*	4*s*	4*p*	4*d*	4*f*	5*s*	5*p*	5*d*	5*f*	6*s*	6*p*	6*d*	7*s*		
H	1	1																			2
He	2	2																			
Li	3	2	1																		8
Be	4	2	2																		
B	5	2	2	1																	
C	6	2	2	2																	
N	7	2	2	3																	
O	8	2	2	4																	
F	9	2	2	5																	
Ne	10	2	2	6																	
Na	11	2	2	6	1																8
Mg	12	2	2	6	2																
Al	13	2	2	6	2	1															
Si	14	2	2	6	2	2															
P	15	2	2	6	2	3															
S	16	2	2	6	2	4															
Cl	17	2	2	6	2	5															
Ar	18	2	2	6	2	6															
K	19	2	2	6	2	6		1													18
Ca	20	2	2	6	2	6		2													
Sc	21	2	2	6	2	6	1	2												first transition series	
Ti	22	2	2	6	2	6	2	2													
V	23	2	2	6	2	6	3	2													
Cr	24	2	2	6	2	6	5	1													
Mn	25	2	2	6	2	6	5	2													
Fe	26	2	2	6	2	6	6	2													
Co	27	2	2	6	2	6	7	2													
Ni	28	2	2	6	2	6	8	2													
Cu	29	2	2	6	2	6	10	1													
Zn	30	2	2	6	2	6	10	2													
Ga	31	2	2	6	2	6	10	2	1												
Ge	32	2	2	6	2	6	10	2	2												
As	33	2	2	6	2	6	10	2	3												
Se	34	2	2	6	2	6	10	2	4												
Br	35	2	2	6	2	6	10	2	5												
Kr	36	2	2	6	2	6	10	2	6												
Rb	37	2	2	6	2	6	10	2	6			1									18
Sr	38	2	2	6	2	6	10	2	6			2									
Y	39	2	2	6	2	6	10	2	6	1		2								second transition series	
Zr	40	2	2	6	2	6	10	2	6	2		2									
Nb	41	2	2	6	2	6	10	2	6	4		1									
Mo	42	2	2	6	2	6	10	2	6	5		1									
Tc	43	2	2	6	2	6	10	2	6	6		1									
Ru	44	2	2	6	2	6	10	2	6	7		1									
Rh	45	2	2	6	2	6	10	2	6	8		1									
Pd	46	2	2	6	2	6	10	2	6	10											
Ag	47	2	2	6	2	6	10	2	6	10		1									
Cd	48	2	2	6	2	6	10	2	6	10		2									
In	49	2	2	6	2	6	10	2	6	10		2	1								
Sn	50	2	2	6	2	6	10	2	6	10		2	2								
Sb	51	2	2	6	2	6	10	2	6	10		2	3								
Te	52	2	2	6	2	6	10	2	6	10		2	4								
I	53	2	2	6	2	6	10	2	6	10		2	5								
Xe	54	2	2	6	2	6	10	2	6	10		2	6								

Electron configurations of the elements

element	atomic number	number of electrons in each sub-shell																			
		1*s*	2*s*	2*p*	3*s*	3*p*	3*d*	4*s*	4*p*	4*d*	4*f*	5*s*	5*p*	5*d*	5*f*	6*s*	6*p*	6*d*	7*s*		
Cs	55	2	2	6	2	6	10	2	6	10		2	6			1					
Ba	56	2	2	6	2	6	10	2	6	10		2	6			2					
La	57	2	2	6	2	6	10	2	6	10		2	6	1		2				lanthanides	third transition series 32
Ce	58	2	2	6	2	6	10	2	6	10	2	2	6			2					
Pr	59	2	2	6	2	6	10	2	6	10	3	2	6			2					
Nd	60	2	2	6	2	6	10	2	6	10	4	2	6			2					
Pm	61	2	2	6	2	6	10	2	6	10	5	2	6			2					
Sm	62	2	2	6	2	6	10	2	6	10	6	2	6			2					
Eu	63	2	2	6	2	6	10	2	6	10	7	2	6			2					
Gd	64	2	2	6	2	6	10	2	6	10	7	2	6	1		2					
Tb	65	2	2	6	2	6	10	2	6	10	9	2	6			2					
Dy	66	2	2	6	2	6	10	2	6	10	10	2	6			2					
Ho	67	2	2	6	2	6	10	2	6	10	11	2	6			2					
Er	68	2	2	6	2	6	10	2	6	10	12	2	6			2					
Tm	69	2	2	6	2	6	10	2	6	10	13	2	6			2					
Yb	70	2	2	6	2	6	10	2	6	10	14	2	6			2					
Lu	71	2	2	6	2	6	10	2	6	10	14	2	6	1		2					
Hf	72	2	2	6	2	6	10	2	6	10	14	2	6	2		2					
Ta	73	2	2	6	2	6	10	2	6	10	14	2	6	3		2					
W	74	2	2	6	2	6	10	2	6	10	14	2	6	4		2					
Re	75	2	2	6	2	6	10	2	6	10	14	2	6	5		2					
Os	76	2	2	6	2	6	10	2	6	10	14	2	6	6		2					
r	77	2	2	6	2	6	10	2	6	10	14	2	6	9							
Pt	78	2	2	6	2	6	10	2	6	10	14	2	6	9		1					
Au	79	2	2	6	2	6	10	2	6	10	14	2	6	10		1					
Hg	80	2	2	6	2	6	10	2	6	10	14	2	6	10		2					
Tl	81	2	2	6	2	6	10	2	6	10	14	2	6	10		2	1				
Pb	82	2	2	6	2	6	10	2	6	10	14	2	6	10		2	2				
Bi	83	2	2	6	2	6	10	2	6	10	14	2	6	10		2	3				
Po	84	2	2	6	2	6	10	2	6	10	14	2	6	10		2	4				
At	85	2	2	6	2	6	10	2	6	10	14	2	6	10		2	5				
Rn	86	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6				
Fr	87	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6		1		
Ra	88	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6		2		
Ac	89	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6	1	2	actinides	incomplete fourth transition series
Th	90	2	2	6	2	6	10	2	6	10	14	2	6	10		2	6	2	2		
Pa	91	2	2	6	2	6	10	2	6	10	14	2	6	10	2	2	6	1	2		
U	92	2	2	6	2	6	10	2	6	10	14	2	6	10	3	2	6	1	2		
Np	93	2	2	6	2	6	10	2	6	10	14	2	6	10	5	2	6		2		
Pu	94	2	2	6	2	6	10	2	6	10	14	2	6	10	6	2	6		2		
Am	95	2	2	6	2	6	10	2	6	10	14	2	6	10	7	2	6		2		
Cm	96	2	2	6	2	6	10	2	6	10	14	2	6	10	7	2	6	1	2		
Bk	97	2	2	6	2	6	10	2	6	10	14	2	6	10	8	2	6	1	2		
Cf	98	2	2	6	2	6	10	2	6	10	14	2	6	10	10	2	6		2		

* The periodic system of the elements can be expressed in terms of electronic configurations as illustrated above. A series of typical elements is characterized by the progressive filling of the outer *s* and *p* orbitals; the transition elements by filling of the *d* orbitals; the lanthanides and the actinides by the filling of the *f* orbitals. The basic rule is that of minimum energy: in the ground state the electrons are arranged, according to certain selection rules, in the orbitals with lowest energy. Small anomalies which are observed are due to factors of secondary importance and do not alter the significance of this interpretation.

disappearance of the ionic bond in solution is a typical example of the action of water, the molecules of which cluster round the two ions and disperse their charge through a very large mass and volume (Fig. 18).

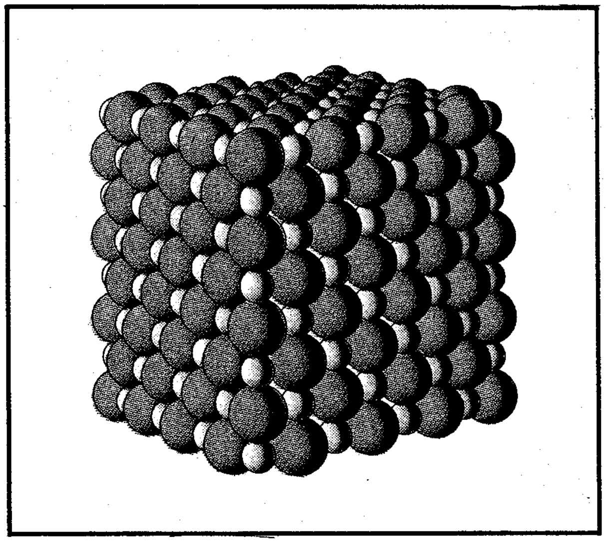
Much more difficult to interpret was, and still is, the covalent bond, the bond which is established, for example, between identical atoms and which is present in the large majority of chemical compounds both organic and inorganic. A valuable proposal was made by Lewis in 1916. He suggested that the covalent bond can be interpreted as the sharing of a pair of electrons between two atoms. For example, two chlorine atoms, which possess 7 electrons in the valence shell, each provide one electron to be shared by both atoms. The two atoms then reach the electronic configuration of argon whilst still retaining their own electrical neutrality (Fig. 19). Covalent bonds can also be formed between different atoms or by sharing two or three pairs of electrons rather than one, forming a double bond and a triple bond respectively.

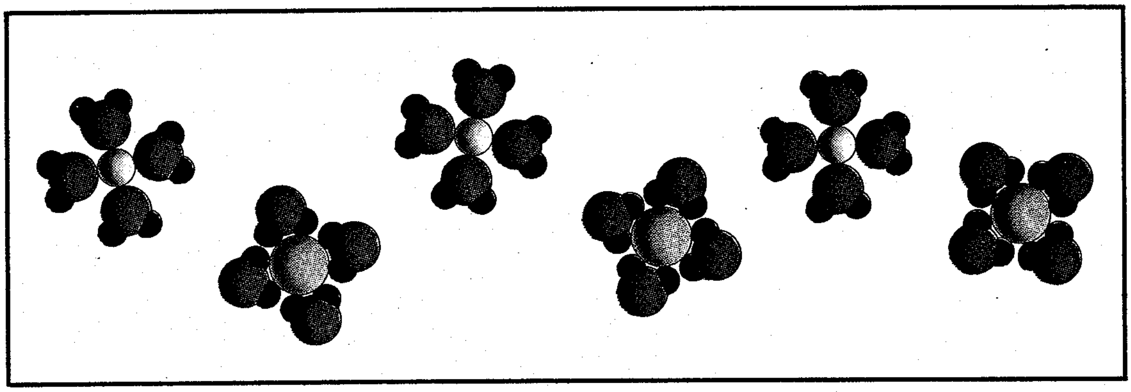
A particular type of covalent bond is the co-ordination or dative bond, in which the shared pair of electrons comes entirely from a single atom particularly rich in electrons. In this case there is also an electrostatic factor superimposed on the covalent bond, due to the separation of the electrical charges within the molecule. The atom which donates the electrons is partially charged in the positive sense and the atom which receives them is charged in the negative sense. Because of this separation of charge the term 'semi-polar bond' is often used.

The factor which, according to the Lewis-Langmuir theory, governs the displacement of electrons in ionic and covalent bonds is the tendency to form particularly stable electronic arrangements, i.e., to reach the electronic configurations of the noble gases (ns^2, np^6). An expression of this fact is the so-called octet rule: each atom achieves maximum stability when it possesses eight electrons in the valence shell. Although many exceptions to this rule are known today, the octet rule allowed a rationalization of the greater part of structural chemistry, for example that of the lighter elements (up to fluorine), and practically all of organic chemistry.

One of the great achievements of the Lewis-Langmuir theory was to have kept the symbolism already in use to indicate bonds: a line for the single bond, two for the double bond and so on, and to have given the lines a physical meaning; each line corresponds to two electrons. To complete these formulae, it is however also necessary to show the lone pairs, those pairs of electrons in the valence shell which each atom does not share with the other atoms in the molecule (Fig. 19) and which play a very important rôle in defining the shape and reactivity of the molecule.

Fig. 18 **The structure of a crystal of table salt, NaCl or sodium chloride, is characterized by alternation of Na^+ and Cl^- ions. The ions are held together by electrostatic forces. When sodium chloride is dissolved in water, the water molecules solvate the ions and, consequently, the interactions between opposite charges are greatly reduced.**





These conventions which we use today to write the formulae of chemical compounds are a sufficient approximation for most purposes. However, compared with forty years ago, they are interpreted in a much more critical fashion because of what has been learnt in the meantime from the quantum-mechanical theory of valency.

The quantum-mechanical interpretation

A molecule is an aggregate of atoms at such small distances from each other that they interact very strongly. A rigorous method of describing this system, analogous to that shown previously for atoms, consists of finding the solutions of the wave equation or, in other words, in drawing an electron density map for all the atoms. A problem of this type cannot be solved exactly, even with the most powerful computers. The Schrödinger equation has only been solved exactly for the hydrogen atom, and for heavier atoms it is necessary to introduce simplifying hypotheses; it is clear that these will be even more necessary if polyatomic molecules are to be studied.

Given these difficulties, several models of varying complexity have been introduced which allow approximate calculations and the prediction of some properties of molecules, starting from a certain amount of data. The electrostatic model predicts the geometry of many compounds in a simple way; the valence bond method, based on concepts of hybridization and resonance, is much used in organic chemistry; the ligand field model has been particularly developed to explain the magnetic, spectroscopic and stereochemical behaviour of co-ordination compounds containing transition metals; and finally, more complete and more general, there is the method of molecular orbitals. The choice of method depends on the type of problem, the degree of approximation desired, the time available, mathematical capabilities and available finance. The cost of a fairly complete calculation on a molecular structure was recently found to be of the order of £4000–£8000 (c. 10–20 thousand U.S. dollars).

We shall obviously not enter into the merit of these proceedings, for the most part comprehensible only to a limited range of specialists. Instead, we shall take a non-systematic path, taking here and there an idea from Pauling and another from Mulliken and retaining as much contact as possible with the symbolism already established.

In the quantum-mechanical treatment also, the covalent bond is interpreted, at least to a first approximation, as the sharing of a pair of electrons between two atoms. The problem consists of describing the position of, or better, the probability of finding, electrons in the various regions of space. When two atomic nuclei are very close it is reasonable to believe that the electronic cloud is strongly perturbed. Thus the shape and size of the orbitals, particularly those directed towards the neighbouring nucleus, will change with the formation of a bond. The electrons which at first moved only around one nucleus experience the attraction of the other as well and their movement is deformed until it involves the second nucleus. The new orbital which describes the state of the electron is called a molecular orbital.

Let us take the simplest case, the hydrogen molecule, H_2. Each atom in its ground (non-excited) state has the $1s^1$ electronic configuration, the electron having spherical symmetry around the nucleus. If the two nuclei are brought together to the equilibrium bond distance, we can write a wave function by quantum-mechanical methods which takes into account interactions of the electrons with the two nuclei. Basically, the new orbital is the sum or the superposition of the two $1s$ atomic orbitals with the same sign but its energy is much less than that of the two separate orbitals. In addition to this orbital, the theory predicts a second with higher energy than the original $1s$ orbitals since the number of molecular orbitals must be equal to the number of atomic orbitals from which they originate.

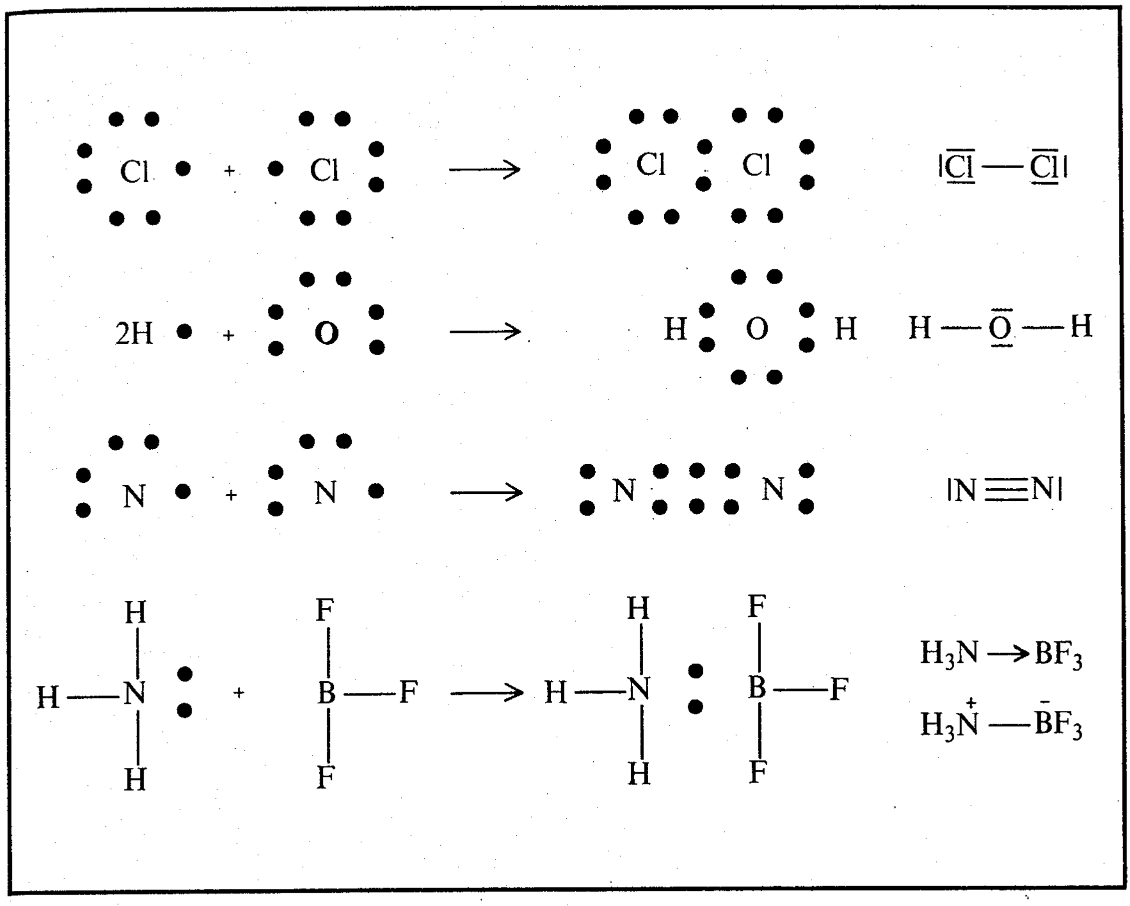


Fig. 19 Some examples of covalent molecules according to the theory of Lewis and Langmuir. To facilitate comprehension the electrons belonging to different atoms are drawn differently. The more usual formulae are on the right. Each line corresponds to two electrons. The covalent bonds are formed from one or more pairs of electrons shared by two atoms. (They are seen in the molecules of chlorine, Cl_2, water, H_2O, and nitrogen, N_2.) In the addition compound between ammonia and boron trifluoride, the bond is of the dative type since the two electrons both come from the nitrogen. The dative bond is indicated by an arrow, or by a line and + and − signs placed respectively on the atom which donates the electrons and on the one which receives them.

This orbital of higher energy (which is called an antibonding or σ^* orbital) is formed by a superposition of orbitals with opposite signs.

We know from Pauli's principle that each orbital can contain two electrons with antiparallel spins. In the H_2 molecule the two electrons present can be placed in the lower energy orbital (Fig. 20). The hydrogen molecule thus has a lower energy than that of the separate atoms and this increase in stability corresponds to the energy of the chemical bond. The presence of two electrons in a low energy molecular orbital (bonding orbital) is the quantum-mechanical expression of the shared doublet of Lewis's theory.

A hypothetical diatomic molecule of helium, He_2, would have a molecular orbital diagram qualitatively quite similar to that of hydrogen. In this case, however, there are four electrons to arrange: two in the bonding orbital and two in the antibonding orbital. The comparison between the energy of the He_2 molecule and that of the two separate helium atoms shows that there is no stabilization in the molecule. He_2, therefore, should not exist in any appreciable concentration. This prediction is in complete agreement with the well known experimental fact that helium and the other noble gases are monatomic, in contrast to hydrogen, oxygen, nitrogen and the other gaseous elements.

The strength of a bond is greater the more the atomic orbitals used in its formation are superimposed. This principle is particularly useful for our purpose which is, above all, to understand why molecules assume certain shapes in space. For geometrical reasons a triatomic molecule is either linear or the nuclei of its atoms lie at the apexes of a triangle; the shape of the triangle, by elementary geometry, is defined by two lengths and an angle.

What is the most suitable angle which corresponds to maximum stability in a molecule? As we have previously stated, the angle must be equal to, or very close to, that existing between the orbitals. The maximum superposition, and thus maximum stability, occurs when the direction of the bond coincides with the direction of maximum elongation of the orbital.

The molecule of hydrogen sulphide, H_2S, offers us a simple example (Fig. 21). The sulphur atom has a Ne, $3s^2$, $3p^4$ electronic configuration, that is to say it possesses one completely filled $3p$ orbital with the other two each containing only a single electron. The combination of the two, singly-occupied, orbitals of sulphur with the singly-occupied hydrogen orbitals leads to the formation of two S—H bonds along the direction of maximum elongation of the p orbitals of sulphur. But as we said on page 43, these are orientated along the Cartesian axes at right angles to each other. The measured angle between the two valencies in hydrogen sulphide is about 93°, very close to the predicted value. The situation is not so satisfactory for water (experimental angle is 104·5°); we shall try to give an explanation for this anomaly later.

This interpretation is certainly at an elementary level. We have, in fact, equated the chemical bonds with electron pairs in certain diatomic orbitals and not with the real molecular orbitals which enclose all the atoms present in a molecule. This approximation is quite legitimate and is widely used since it permits a more rapid and simpler study of very complex molecular structures.

We have already mentioned the problem of the valence angle of water and the difference of more than 14 degrees between the observed and predicted valence angles. There is a still bigger question: how to explain the tetravalency of carbon and the tetrahedral arrangement of the carbon valencies, the two bases on which organic chemistry has been built?

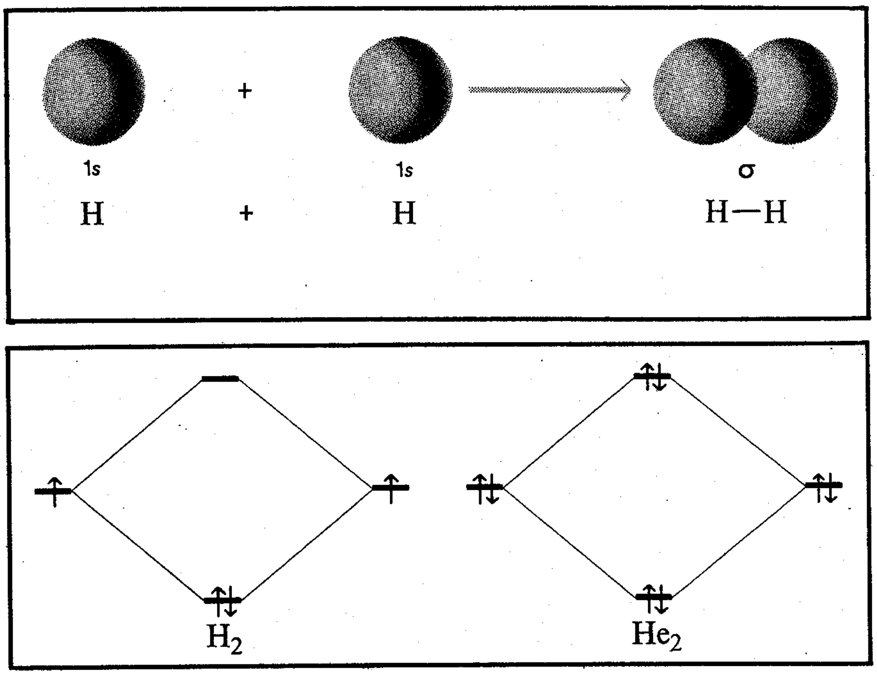


Fig. 20 **Above: the combination of two *s* orbitals to form a σ bond. The maximum electron density is along the line joining the two atoms. Below: energy levels of the molecular orbitals. The orbital with lower energy is called a bonding orbital and the other an anti-bonding orbital. The electrons arrange themselves in pairs in the different orbitals with anti-parallel spins, starting from the levels with the lowest energies. On the left, the energy diagram of a hydrogen molecule, H_2, and, on the right, that for a hypothetical molecule of helium.**

The formation of four identical bonds by the carbon atom can be explained if, instead of *s* and *p* orbitals (different from each other), identical orbitals are postulated, derived from them by mathematical procedures. (It should be remembered that orbitals are purely mathematical expressions.) By suitably combining an *s* orbital and three *p* orbitals, four hybrid sp^3 orbitals are obtained, arranged in a rigorously tetrahedral manner (Fig. 22). The carbon bonds can be interpreted in an analogous way to that previously described for hydrogen sulphide but by substituting the hybrid sp^3 orbitals for the pure *s* and *p*. The methane molecule, CH_4, contains four C—H bonds in which the electrons lie in bond orbitals of the sp^3-s type; carbon tetrachloride, CCl_4, has sp^3-p bond orbitals.

Depending on the number and type of the original bond orbitals we can obtain different types of hybrid orbitals with different geometrical arrangements. For example, in boron trifluoride, BF_3, the electrons of the bonds are placed in sp^2-p orbitals in which the three sp^2 hybrid orbitals of boron are arranged in a plane at 120° to each other. In beryllium chloride, $BeCl_2$, in the gaseous state, beryllium has sp^2 hybridization, the two bonds being co-linear and in opposite directions (valence angle 180°).

All the bonds which we have described, in which the electrons are placed in bi-nuclear orbitals of the type *s*-*s*, *s*-*p*, sp^3-p, etc., are called

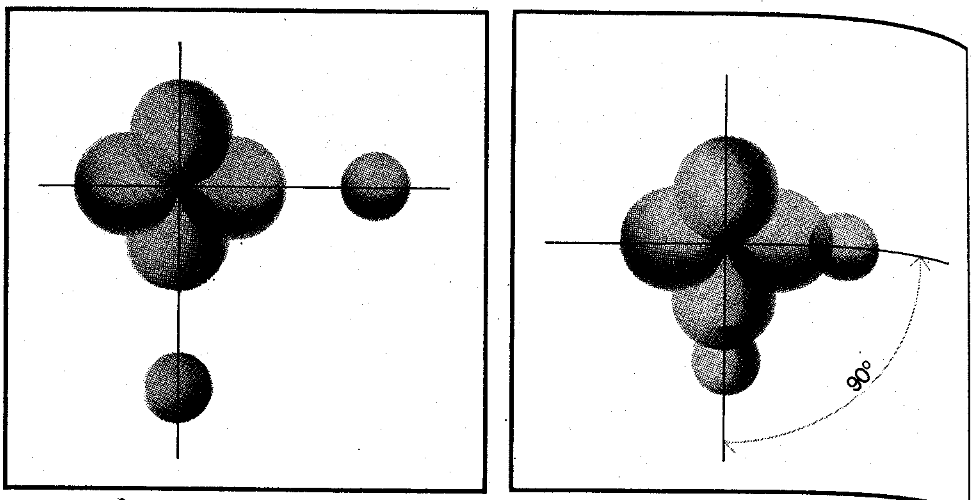
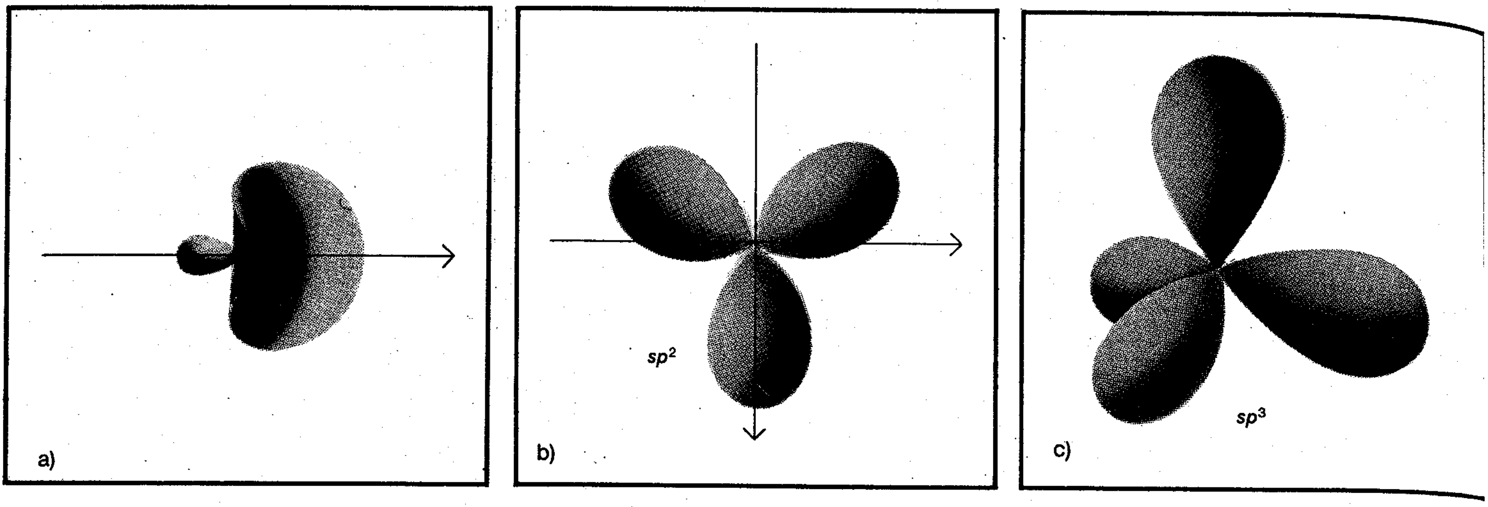


Fig. 21 The combination of two sulphur $3p$ orbitals and the $1s$ orbitals of two hydrogen atoms. The p orbitals are orthogonal to each other; this gives rise to the fact that the angle between the bonds in hydrogen sulphide, H_2S, must also be approximately 90°.

Fig. 22 The hybrid orbitals have a two-lobed shape with one lobe bigger than the other (*a*). The two *sp* hybrid orbitals point in opposite directions (angle of 180°); the three sp^2 orbitals are arranged in a plane at 120° (*b*). The four sp^3 orbitals have a tetrahedral arrangement (*c*).



σ bonds. Their most important characteristic is that of giving the maximum electron density along the line joining the two atomic nuclei. But there is a second type of covalent bond, called a π bond, in which the electron density is at a maximum away from this line. The π bond has its origin in the lateral approach of two parallel p orbitals and is present in unsaturated compounds together with a σ bond. The structure of ethylene is shown in Fig. 23.

Ethylene, C_2H_4, has the structural formula $CH_2{=}CH_2$, i.e., it contains a double bond between the two carbon atoms. Let us first look at the skeleton of this molecule made from the σ bonds. The two carbon atoms have sp^2 hybridization and form five bonds in all, four with the hydrogen atoms and one between themselves, with angles of 120° for the bonds around each carbon atom. In addition, each carbon atom possesses a p orbital with a so-far unshared electron. If we rigorously fix the six atoms in a plane, the two p orbitals are parallel and are in the best position to form a π-bond into which two electrons may enter. The probability of finding the electrons is a maximum above and below the plane of the molecule.

The structure of acetylene, $CH{\equiv}CH$, can be interpreted analogously. The carbon atom is *sp* hybridized and the bonds between C and H and between C and C are linear; the p_x and p_y orbitals, each containing an electron, combine with those of the other carbon atom to form two π-bonds which, together with the σ, form the characteristic acetylenic triple bond.

This interpretation of the structure of unsaturated compounds accounts very well for the chemical, stereochemical and spectroscopic properties of such compounds. This is not the only possible model, however, and with very different procedures it is possible to arrive at substantially similar results.

Delocalization of electrons and resonance

Unsaturated compounds are very widespread in both organic and inorganic chemistry. Unsaturation does not always involve carbon-carbon double bonds, which we have considered so far, but is also found in bonds between carbon and oxygen, oxygen and nitrogen, and between other elements. However, the detailed interpretation does not differ greatly from that given above. Acetone, for example, a much used solvent, contains a C=O double bond. Because of the different electronegativity of the two atoms (oxygen is more electronegative, or attracts electrons more strongly, than carbon) the electronic cloud is not arranged in a symmetrical way with respect to the two atoms but is displaced more towards the oxygen. The particular reactivity of the C=O group is derived from this fact and

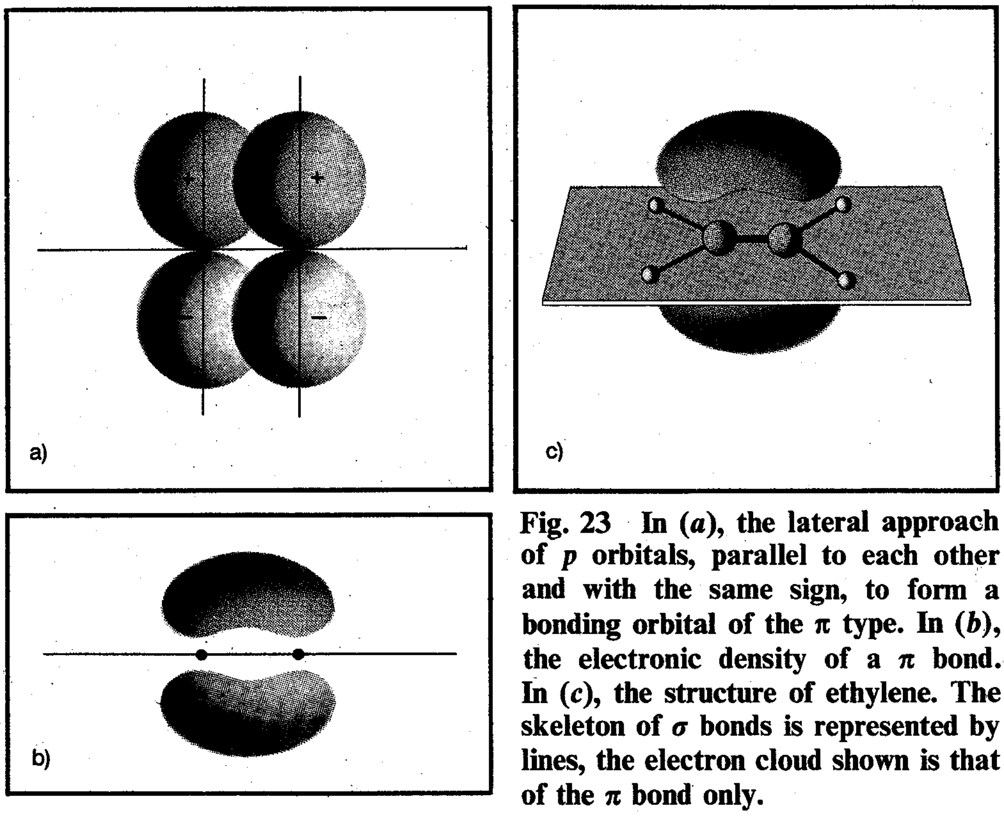


Fig. 23 In (*a*), the lateral approach of *p* orbitals, parallel to each other and with the same sign, to form a bonding orbital of the π type. In (*b*), the electronic density of a π bond. In (*c*), the structure of ethylene. The skeleton of σ bonds is represented by lines, the electron cloud shown is that of the π bond only.

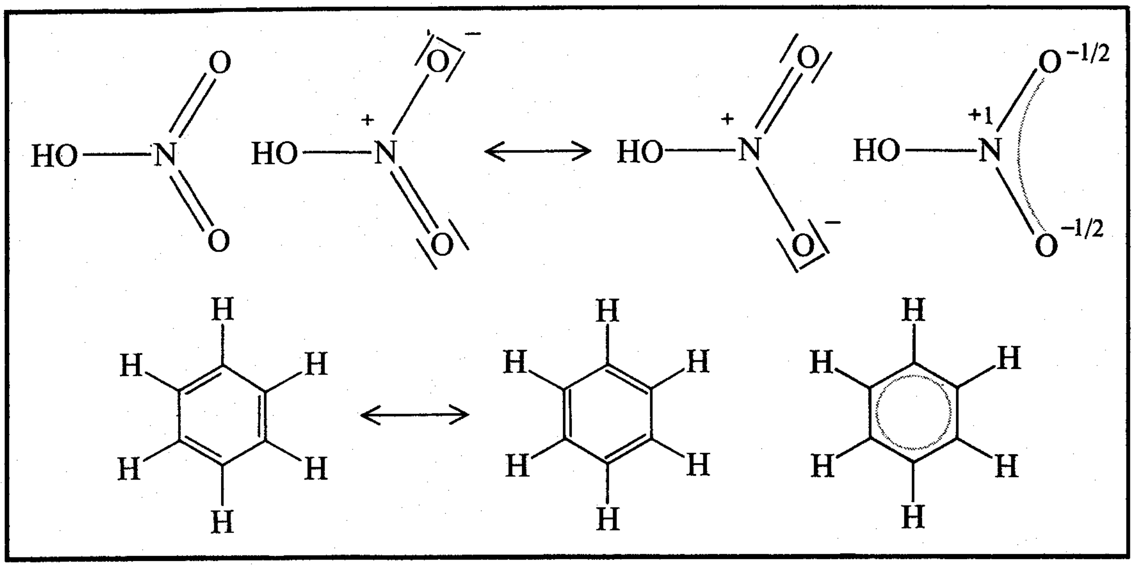


Fig. 24 Above, from the left: a now forgotten formula for nitric acid (in which the nitrogen was considered pentavalent), two limiting resonance forms which are different to each other only in the arrangement of the oxygen-nitrogen bonds, and the formula with delocalized electrons, intermediate with respect to the limiting forms. Below: two limiting resonance forms of benzene corresponding to the Kekulé formula, and the formula of benzene with complete hexagonal symmetry.

it is characteristic of several classes of compounds (ketones, aldehydes, acids, esters, etc.).

There are, however, other classes of compounds for which our treatment is still not sufficient. Nitric acid, one of the most powerful acids known, is a typical representative. Its empirical formula is HNO_3; in the classical theory the central nitrogen is pentavalent, having a single bond to the OH group and two double bonds to the other atoms of oxygen (Fig. 24). In electronic terms this would require the presence of ten electrons in the valence shell of nitrogen which would be contrary to the octet rule. According to Lewis, nitric acid must be formulated with one double bond $N{=}O$ and one semi-polar bond between the nitrogen and the other oxygen. The octet is thus retained but an arbitrary distinction is introduced between the two oxygen atoms which in reality are quite equivalent.

To deal with cases of this type, Pauling introduced, around 1930, the idea of resonance structures. Nitric acid, for example, can be written with two Lewis formulae, identical except in the arrangement of the bonds between nitrogen and oxygen; but neither of these represents the real state of the molecule. The molecule is then said to 'resonate' between the two extreme forms or to be a 'resonance hybrid' of the two forms.

What physical significance can be attached to the term resonance hybrid? It certainly does not mean that half the molecules are of one type and half of another; nor does it mean that the molecule possesses the first structure for a certain time and then transforms into the other. It simply means that the structure of each molecule is intermediate between the two. There is no alternation between a single and a double bond but the π electrons are distributed or *delocalized* in the two bonds and confer on these partial multiple-bond character. A resonance hybrid, can be compared to a mule, which although derived from a horse and an ass is not half horse and half ass but is a blend of the two.

A famous case of the application of the resonance theory is provided by benzene (Fig. 24). The structure of this cyclic compound was first formulated by Kekulé. Benzene can be considered to be made from a ring with six carbon atoms alternately bonded to each other by single and double bonds. However plausible this structure may be, it does not explain several characteristics of benzene, for example, its hexagonal symmetry and its great stability. In particular a system of alternating (or 'conjugate') double bonds should have a very high reactivity. But benzene is relatively unreactive. Here also, therefore, we must consider the two possible Kekulé formulae as limiting resonance forms and we say that the real state of the molecule is intermediate between these. The C—C bonds all have the same length, intermediate between those of normal or single and double bonds, and the distribution of the electrons is homogeneous in all the bonds. Moreover, the real energy of the molecule is much less than that calculated for the limiting forms (about 40 Kcals per mole) and the stability and chemical inertness of benzene can be explained as a result of this resonance.

The wide acceptance of the resonance theory in the last thirty years has arisen from its great simplicity in use and from the fact that it required no modification of the existing chemical symbolism. A great number of important structural problems have been solved by its help without particular difficulty, although only on a qualitative or semi-quantitative basis.

However, owing to the need for a more quantitative treatment, theoretical chemists have turned more towards the theory of molecular orbitals which, as we shall see in a later chapter, faces these problems in a totally different way. With the arrival of electronic computers, the mathematical difficulties which had prevented a wider use of this treatment were largely overcome and it is the consequent possibility of making calculations on the biggest molecules that has made the method of molecular orbitals the most refined theoretical instrument for studying chemical structures. The international recognition given to Robert S. Mulliken (Nobel prize 1966), one of the scientists who has contributed most to its creation, provides a significant demonstration of this fact.

There is still a great achievement of Linus Pauling and his school to be mentioned, that of having accustomed entire generations of chemists to read behind the traditional formulae in a deeper and more critical way. The significance of the classical formulae for nitric acid and benzene has been completely changed although they are still drawn in the old way. From now on it will be sufficient to write benzene with only one of the Kekulé formulae because we clearly understand its significance.

The geometry of molecules

This long discussion of modern theories of the chemical bond has furnished some elements for the better understanding of stereochemical phenomena. We have examined the methane molecule and given an electronic interpretation of its tetrahedral structure. In the same way we may ask ourselves if it is possible to predict the shape of other organic and inorganic molecules. How can the molecular structure of water, ammonia and so on, be explained?

The shape of a molecule is determined in the first place by the number of electrons present in the valence shell of each atom (and especially of the central atom). We recall two cases already treated: gaseous beryllium chloride, $BeCl_2$, has a linear structure (valency angle 180°); water, H_2O, on the other hand, has an angular structure (valency angle 104·5°). The basic difference between the two molecules arises from the presence of the two unshared electron pairs on the oxygen which imposes a much narrower angle.

To understand this we can choose a simple electrostatic model. The problem in which we are interested can then be expressed thus: what is the best way to arrange electrical charges all having the same signs on the surface of a sphere so that they have the maximum stability? The possible arrangements depend on the number of charges: if there are two charges, they will be in diametrically opposite positions; three charges, on the other hand, will be placed

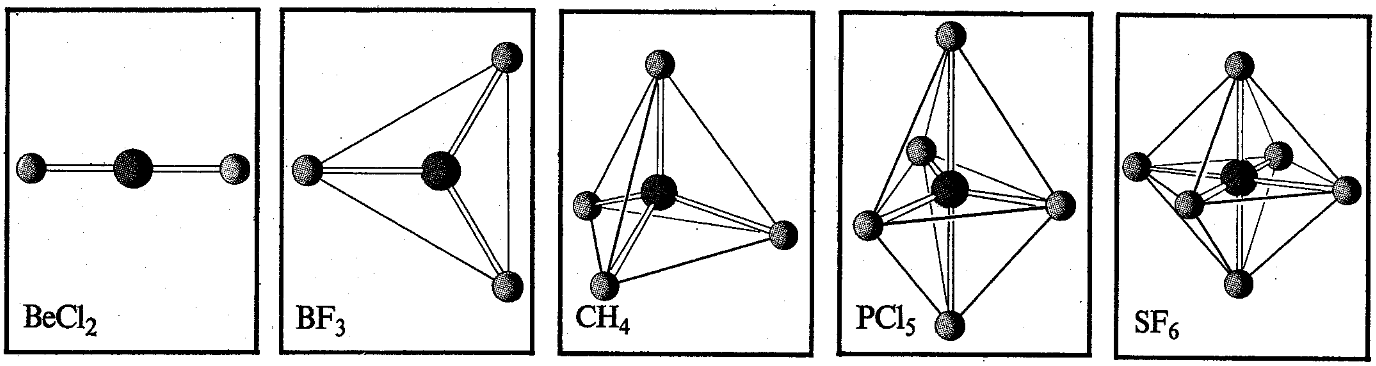


Fig. 25 When the central atom of a molecule is surrounded by two, three, four, five or six atoms and the molecule does not contain lone pairs of electrons, the resultant shape is respectively linear, planar, triangular, tetrahedral, trigonal bipyramid and octahedral, disregarding deformations due to the different nature of the bonded atoms.

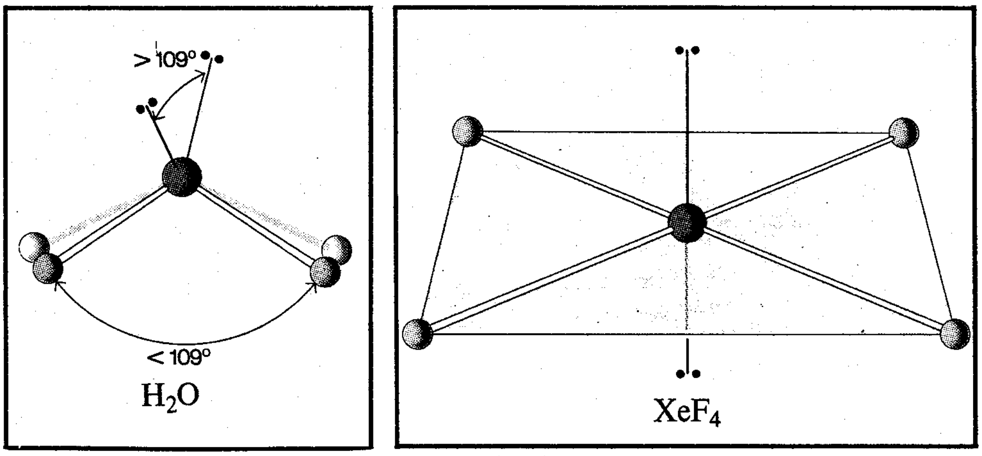


Fig. 26 If lone pairs of electrons are present, these tend to move as far apart as possible from each other. In the water molecule this factor leads to a deformation of the valence angle – it is about 5° smaller than predicted. In xenon tetrafluoride, a noble gas compound, the electron pairs are arranged at the opposite vertices of an octahedron.

on the circumference of a great circle at 120° to each other; four will be at the vertices of a regular tetrahedron. In the case of five charges the most stable arrangement corresponds to a triangular bipyramid, while six charges will have an octahedral arrangement (Fig. 25).

It can be seen that particular hybrid orbitals correspond to the arrangements obtained with the electrostatic method. The same result is also reached by using the method of valence bonds and constructing a series of orbitals, equivalent or almost equivalent to each other, each one of which can give rise to a σ bond and which is thus occupied by two electrons. The most common hybrid orbitals – passing from two to six pairs of electrons – are respectively: sp, sp^2, sp^3, sp^3d, sp^3d^2. The electronic arrangements and hybridizations just listed are valid for the non-transition elements. For the transition metals it is necessary to consider a square structure as well (dsp^2 hybridization); but the phenomenon is more complex and is generally treated by other methods.

The first three forms of hybridization (sp, sp^2 and sp^3) are the only possibilities for the elements of the first short period, to which the octet rule applies rigorously. From sodium onwards it is possible to accommodate more than four pairs of electrons and more complex hybridizations are found. In phosphorus pentachloride, PCl_5, the phosphorus atom forms five σ bonds and thus has the shape of a trigonal bipyramid. Sulphur hexafluoride, SF_6, (a gas with very strange properties: it is chemically very inert and because of its dielectric characteristics is used in high tension switches) has an octahedral structure with twelve electrons around the sulphur atom ($sp^3\,d^2$ hybridization).

The presence of unshared pairs of electrons is another important facet of electronic structure. Although occupying one of the orbitals, the lone pair has a negligible volume and thus the molecular geometry is reduced, for example, from a tetrahedral shape to that of a triangular pyramid (if there is only one lone pair as in ammonia), or to the V-planar shape (if there are two lone pairs as in water). Secondly, the strong repulsions that the lone pairs exert on the neighbouring electron-clouds, both other lone pairs and bonds, can produce shapes which are deformed compared to those predicted by the simple approach. The exact molecular structure of water must be attributed to this effect. We saw that to a first interpretation the valency angle of water should be 90°. According to the model just discussed, the angle should instead be 109·5°, the tetrahedral angle. There are eight electrons around oxygen, two lone pairs and two σ bonds. The presence of the two lone pairs reduces the space available for the bonds and the angle closes up to a position of equilibrium at about 104·5° (Fig. 26).

It would be possible to continue giving examples showing the general validity of this method. However, we shall close with just one problem which caused a great sensation in recent years. In 1962 a compound of a noble gas was prepared for the first time, xenon hexafluoroplatinate. Chemists had always placed great faith in the particular electronic stability of the noble gases and there was some surprise that even these could react. In an age of critical revision like ours this fact shows us just how relative are our judgments and predictions. Today we know a large series of xenon fluorides and oxides endowed with exceptional reactivity. What is their justification at the electronic level? We have repeatedly said that the octet rule is not absolute; consequently, it is possible to have other stable electronic configurations in addition to those of the noble gases. If this is possible, for example for sulphur, there is no reason why it cannot be possible for xenon. Sulphur hexafluoride itself represents a useful model for the structure of one of the more important noble gas compounds, xenon tetrafluoride, XeF_4. This molecule has 36 electrons in the valence shell: 8 of these are involved in the Xe-F σ bonds, another 24 cluster around the fluorine atoms (according to the octet rule) and the remaining 4 are arranged around the xenon atom in two pairs. Four bonds and two lone pairs lead to an octahedral arrangement of charges exactly similar to that of SF_6 but owing to the repulsions exerted between them the two lone pairs prefer to lie in diametrically opposite positions (Fig. 26). For XeF_4 a square planar structure is thus predicted which has been fully confirmed by crystallographic analysis.

We began this chapter with the name of Mendeleev. In his time the noble gases were neither known nor could their existence be predicted. Today we know that they are not, in fact, inert, and many of their compounds have been prepared. The history of modern science has taught us to see that all knowledge at a given time is just a transient view of a process of almost continuous development. We have talked about the Bohr atom, the octet rule, resonance and molecular orbitals: many of these terms already belong to the past. Today the quantum-mechanical theory seems to give the best interpretation of atomic and molecular reality. But what will become of it when faced with the criticisms and problems of tomorrow?

III

The shape of molecules

As is well known, the study of chemistry is generally subdivided into two parts, inorganic chemistry and organic chemistry. Organic chemistry, to a first approximation, consists of the derivatives of carbon. The actual significance of these terms, organic and inorganic, has very little to do now with their etymology. They were introduced by Berzelius in 1807 and were based on a vitalistic criterion: compounds derived from living organisms being differentiated in a radical manner from those of the non-living world. For their formation the intervention of a *vital force* was proposed – a force which could not be reproduced in the laboratory. On the other hand, it was believed that the synthesis of inorganic compounds required only inanimate substances and forces could be reproduced at will.

This dualist view had a short life, little more than twenty years in fact. Friedrich Wöhler, in a now famous experiment, started from mineral substances and synthesized an organic compound, urea, one of the most important substances in animal metabolism. Although the hypothesis of the vital force had collapsed, the distinction between organic and inorganic chemistry remained, because of the differences in properties and structure between compounds of carbon and those of the other elements. The former are often liquids or low-melting solids, easily combustible, heat-sensitive and usually sparingly soluble in water but soluble in organic solvents like alcohol, ether or benzene. In structure, they are composed of chains or rings formed from atoms of carbon bonded to each other. For this reason an enormous number of carbon compounds exist.

While it is true that these criteria are substantially valid, it must be pointed out that the actual situation is more complex. With increased understanding of inorganic chemistry it was seen that other elements, like silicon (Si), and pairs of elements, like boron and nitrogen (B, N), can also give rise to chains and rings of an 'organic' type. Mention is made today, in science fiction circles, of a hypothetical extra-terrestrial life based on silicon. In reality, chemistry is a unitary science and the division into two parts is a matter of convenience with the advantages and disadvantages associated with any convention.

Having settled these preliminaries, let us now try to face in successive stages a problem of great importance: how is a molecule, in particular an organic molecule, made and what is the relationship between the formula which we write and the actual structure of the compound.

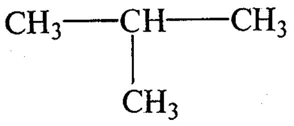
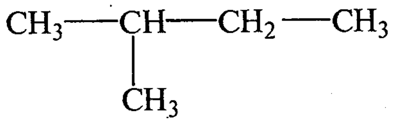
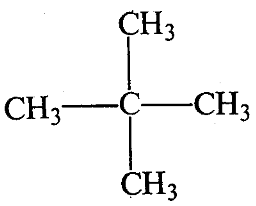
Isomerism or the multiplicity of structures

We have repeatedly indicated that, in the majority of its compounds, carbon is tetravalent i.e., it can bond itself to four other atoms. Let us examine the simplest series of organic compounds, the non-cyclic saturated hydrocarbons (Table IV). In methane, CH_4, the carbon is bonded to four hydrogens; in ethane, CH_3-CH_3, each carbon atom is bonded to three hydrogens and another carbon; in propane, CH_3-CH_2-CH_3, the central carbon is bonded to two hydrogen and two carbon atoms. In compounds with greater structural complexity one may also find carbon atoms bonded to a single hydrogen and three carbon atoms, or even carbon atoms bonded to four other carbon atoms.

The change from a compound to that immediately following it, its homologue (for example, the change from a compound with two carbon atoms to one with three), clearly takes place by substituting a —CH_3 (or methyl) group for a hydrogen atom. Since this substitution can be carried out by starting in any position and continuing in all possible directions, the number of compounds having the same empirical composition, i.e., an equal number of hydrogen and carbon atoms, grows enormously with the increase in the number of atoms. However, one should not forget that each particular structure corresponds to a chemical compound with its own very precise individuality. Thus there are 2 saturated hydrocarbons with four carbon atoms (butanes), 3 with five atoms (pentanes), 5 hexanes, 9 heptanes and 75 decanes (C_{10}); more than 360000 saturated hydrocarbons are possible for twenty carbon atoms and more than 4 thousand million with the formula $C_{30}H_{62}$.

Introducing atoms other than carbon and hydrogen into the molecule increases the number of isomers, that is to say compounds with the same empirical formula but different structures. There is only one propane, but two different propyl alcohols, primary or *normal* CH_3-CH_2-CH_2OH and secondary or *iso* CH_3-CHOH-CH_3 and the properties of the two are distinctly different. The same empirical formula, however, also characterizes another compound with a completely different structure and reactivity: methyl ethyl ether, CH_3-O-CH_2-CH_3. The oxygen atom here is inserted in the principal chain and is no longer bonded to a hydrogen atom; the characteristics of weak acidity shown by the two propyl alcohols (the word acid in chemistry having a rather broad significance and one rather removed from conventional usage) do not occur in ether. Again, while the two alcohols have a relatively low volatility (boiling between 80° and 100°) and a strong alcoholic smell, methyl ethyl ether has a narcotic action similar to that of normal ether (diethyl ether) and cannot be kept in the liquid state except in a cylinder or closed bottle under pressure. This difference between alcohols and ethers is a typical example of structural isomerism while the preceding example between primary and secondary alcohol is better described as positional isomerism. We shall see that other types of isomerism exist and further complicate the picture.

Table IV. Phenomena of isomerism in hydrocarbon chains*

C_4H_{10}	$CH_3—CH_2—CH_2—CH_3$	*n*-butane
	 $CH_3—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—CH_3$	*iso*-butane
C_5H_{12}	$CH_3—CH_2—CH_2—CH_2—CH_3$	*n*-pentane
	 $CH_3—\underset{\displaystyle CH_3}{\underset{\vert}{CH}}—CH_2—CH_3$	*iso*-pentane (2-methylbutane)
	 $CH_3—\overset{\displaystyle CH_3}{\overset{\vert}{\underset{\displaystyle CH_3}{\underset{\vert}{C}}}}—CH_3$	*neo*-pentane (2,2-dimethylpropane)

* As an example of structural isomerism, we show the formulae of two, saturated, acyclic hydrocarbons with four carbon atoms (*normal*-butane and *iso*-butane) and of three isomers with five atoms (*normal*-pentane, *iso*-pentane and *neo*-pentane).

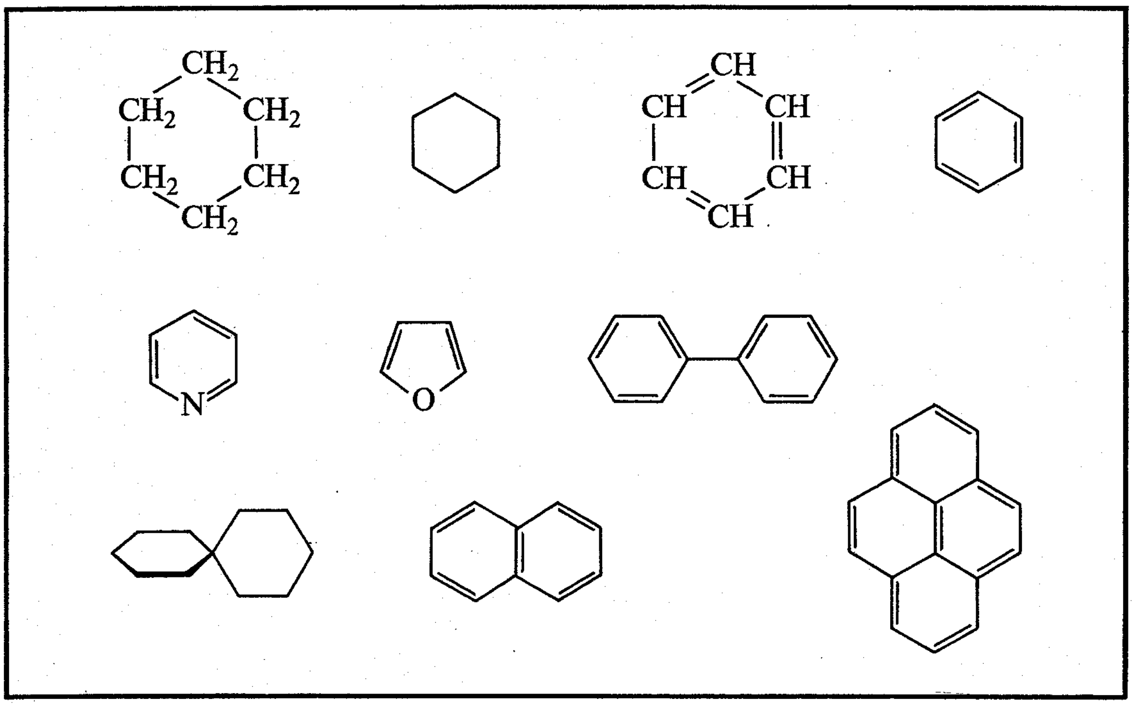


Fig. 27 Formulae for the structures of some cyclic compounds. In graphical representation the carbon atoms which form part of the ring are often omitted. From the upper left: two formulae for cyclohexane and two for benzene, and the formulae for pyridine and furan. These are followed by the formulae of some polycyclic compounds: biphenyl, spiro(5,5)undecane, naphthalene and pyrene.

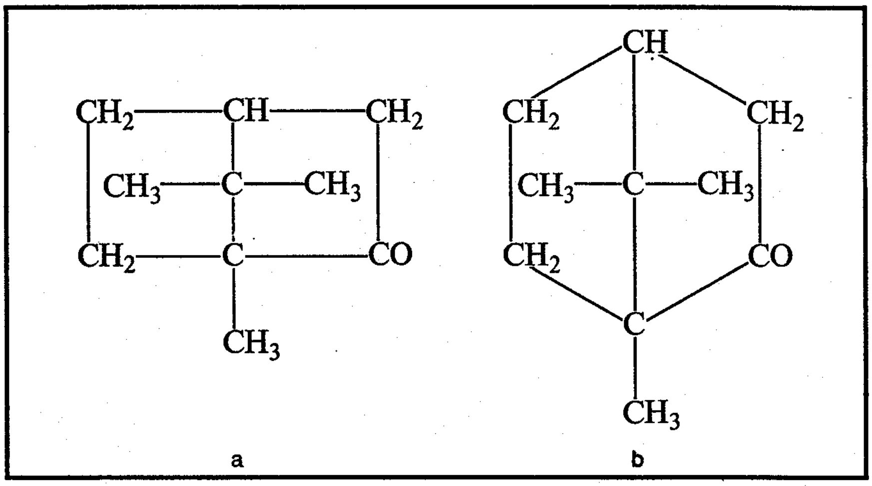
About three-quarters of actual research in organic chemistry concerns compounds whose structures contain sequences of atoms in the form of rings. The possibility of cyclic compounds further multiplies the number of compounds of carbon (Fig. 27). There are homocyclic or heterocyclic compounds, depending on whether the ring is formed only from carbon atoms or whether it also contains other atoms (nitrogen, oxygen, sulphur, phosphorus, boron, etc.); monocyclic or polycyclic compounds, depending on the number of rings present in the molecule. These latter can be of a spiran type or with fused, condensed or bridged rings.

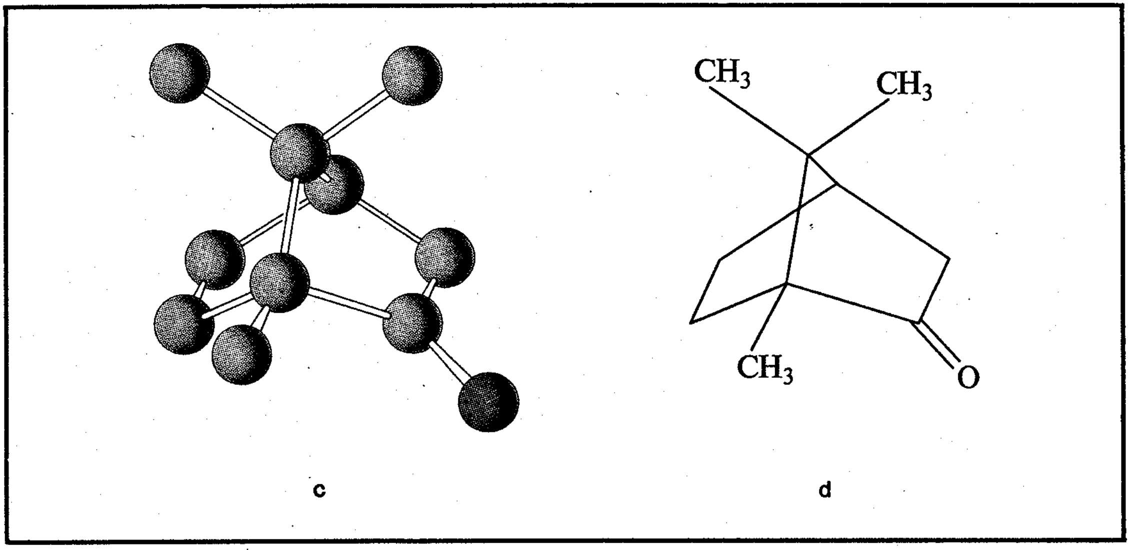
Obviously the formulae drawn for such compounds must indicate their three-dimensional structure. For many years the diagrammatic representation of organic compounds concerned itself exclusively with the chemical bonds between atoms. The use of such representation meant that much information about reactivity and structure was not explained or was concealed (Fig. 28).

Under the pressure of greater theoretical requirements and new experimental techniques this situation changed and today there are many ways of writing – and of reading – chemical formulae. The important problem is to establish the level of knowledge required in a particular case. The more one goes into detail and wishes to explain the different behaviour of similar compounds, the more necessary it is to have an exact knowledge of the structure and thus of the shape of the molecule.

The different types of stereoisomerism

The essential characteristics of a molecular structure are the so-called atomic co-ordinates. Let us suppose we have a set of Cartesian axes





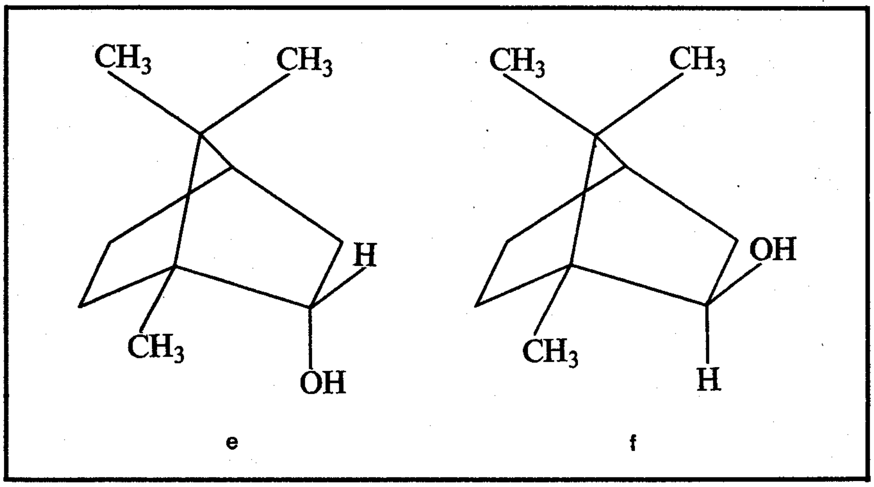


Fig. 28 **The old formulae of camphor (*a*, *b*) gave little idea of its real structure (*c*). The formula (*d*) is a fairly good graphical representation. It clearly indicates the non-planarity of the molecular skeleton and the possibility of isomerism in camphor derivatives. Borneol (*e*) and *iso*-borneol (*f*), the two alcohols obtained by reduction of camphor, are two spatial isomers of the *endo-exo* type: the hydroxyl is internal in one case and external in the other, with respect to the ring system, and has notably different reactivity in the two compounds.**

borneol (*f*), the two alcohols obtained

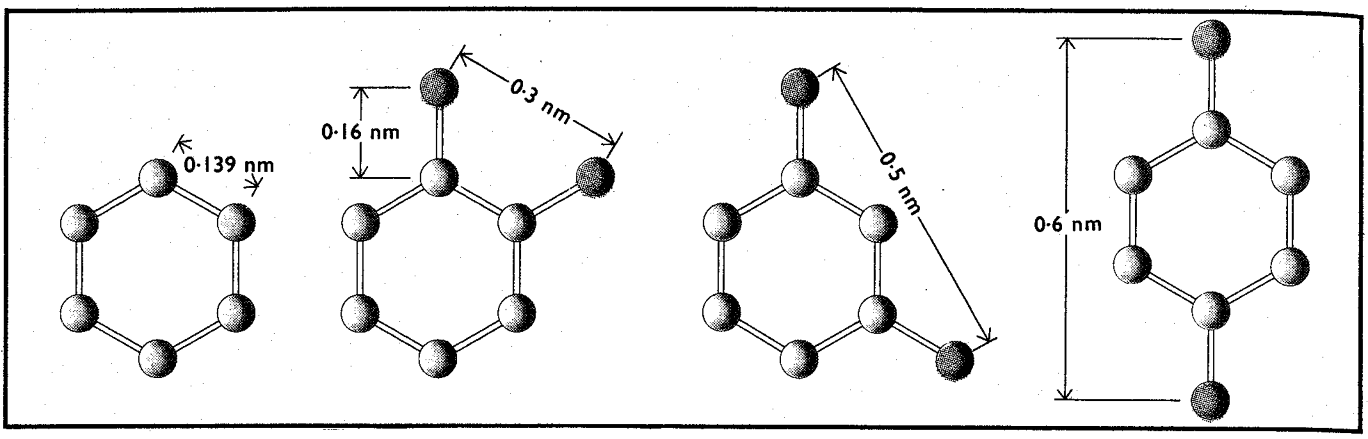


Fig. 29 Models of benzene, 1,2 or *ortho*-dichlorobenzene, 1,3 or *meta*-dichlorobenzene and 1,4 or *para*-dichlorobenzene. The most significant interatomic distances are also indicated.

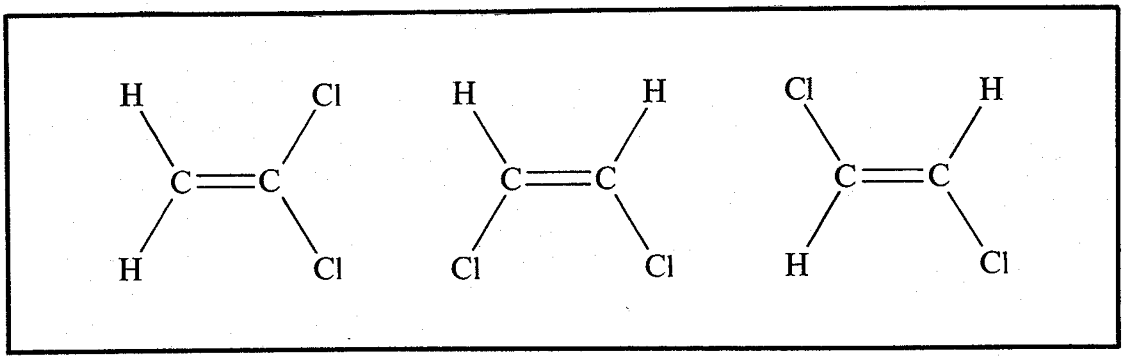
x, *y* and *z*. The position of an atom will be defined by certain values of *x*, *y* and *z*, just as the position of an aeroplane or satellite is given by its longitude, latitude and height.

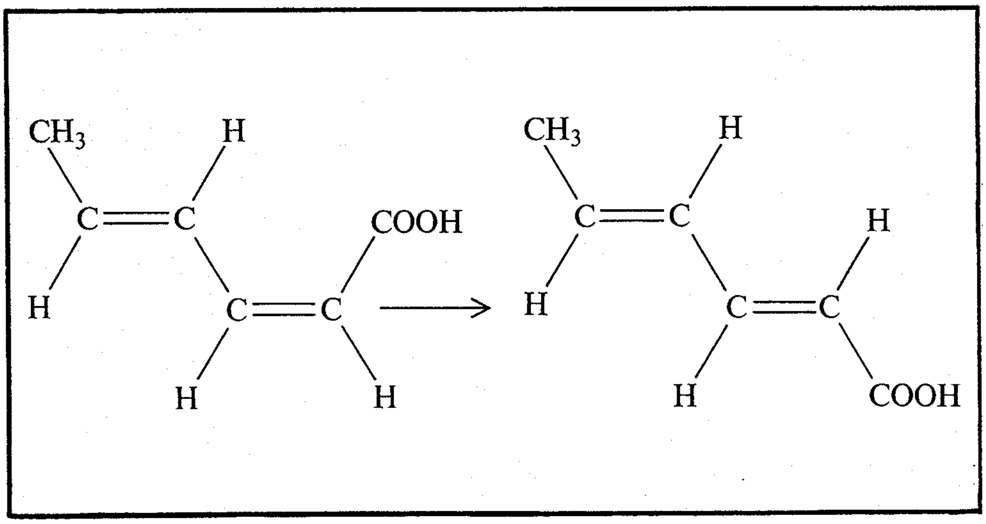
The experimental technique for determining atomic co-ordinates, X-ray diffraction, has been known for fifty years but the difficulties of calculation associated with it hindered for a long time its application to complex chemical problems. It is only in recent years, with the development of high-speed electronic computers, that X-ray diffraction has been able to realize its great potential value.

However, knowledge of atomic co-ordinates has not much interested chemists – apart from specialists in crystallographic investigations. This is because, before these data can have any value, they must be translated into normal language which, for the chemist, can signify the presence of a bond between two atoms and then, for those desiring more detail, the lengths of bonds, the angles between the bonds, and the angles of rotation around the bonds.

The general agreement existing between the data extracted by X-ray diffraction methods and the hypotheses based on the evidence of chemical behaviour allows us to say with certainty that a bond exists between two atoms when their distance apart lies between certain experimentally determined limiting values. For example, a bond exists between two carbon atoms if they are no further apart than 0·16–0·18 nm (1 nm or nanometer = 10^{-9} meters = 10Å). A further refinement is possible. Distances lying between 0·145 and 0·155 nm generally indicate the presence of a single C—C bond; distances between 0·13 and 0·14 nm are in agreement with the existence of a C═C double bond; while distances less than 0·13 nm must be attributed to a C≡C triple bond.

The data on the lengths of bonds are also accompanied and confirmed by values of the valence angles. As stated in the preceding chapter, there is, at least to the first approximation, a relationship between the type of co-ordination of an atom and its valence angles. For a fourfold co-ordination, corresponding to sp^3 hybridization, the theoretical valence angle is 109° 28′; for a threefold co-ordination (sp^2 hybridization) the angle is 120°; while for a twofold co-ordination (sp) the theoretical angle is 180°. Apart from certain special cases, these rules have been verified to within about plus or minus 5–7 degrees. A planar, regular hexagonal structure of carbon atoms positioned at a distance of 0·139 nm from each other corresponds to the compound benzene, C_6H_6, the compound which is the basis of aromatic chemistry. If, in addition to this hexagon, X-ray (or electron) diffraction reveals the presence of another two atoms, e.g., chlorines positioned about 0·16 nm from the carbon atoms and at about 0·30 nm from each other, the compound is identified as *ortho*-dichlorobenzene (the 1,2 isomer); if the two chlorine atoms





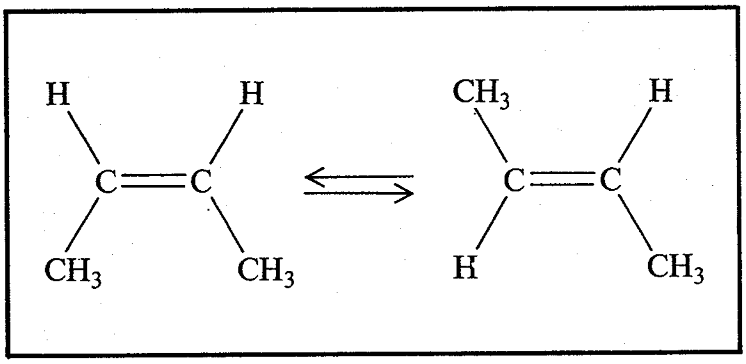


Fig. 30 Above: the three dichloroethylenes. The first compound is structurally different from the others, while the second and third are stereoisomers, i.e., are different from each other with regard to the arrangement of their valences in space. *Cis-trans* isomerism also exists in compounds with two or more double bonds. In the centre, *cis*, *trans*-sorbic acid and *trans*, *trans*-sorbic acid. The two compounds indicated at the bottom, *cis*- and *trans*-2-butene, are stable but capable of interconversion in the presence of catalysts.

are about 0·50 nm apart, the compound is *meta*-dichlorobenzene (the 1,3 isomer); if instead the distance is still greater (*c*. 0·60 nm) the compound examined is *para*-dichlorobenzene (1,4) (Fig. 29).

We are still in the field of positional isomerism but it is a short step to the first example of stereoisomerism or, in other words, spatial isomerism. Let us consider the three different isomers of dichloroethylene (Fig. 30). The first of these has two chlorine atoms bonded to the same carbon atom (l,l-dichloroethylene); the other two, although different from each other, have the same name, 1,2-dichloroethylene, and have the same schematic formula $CHCl{=}CHCl$.

The difference between these two compounds lies only in the different positions of the two chlorine atoms with respect to the molecular framework. In the first, the two atoms are on the same side with respect to the double bond and, in the second, they lie on opposite sides. The first is called a *cis* stereoisomer and the second a *trans*. That an isomerism of this type can exist arises from the rigidity of the double bond which, as we have seen, we can consider as being formed by a σ bond and a π bond. A rotation of one of the two carbon atoms around the central bond would transform one isomer into the other but this rotation is possible only if the π bond is broken. A process of this type is notably endothermic (i.e.,

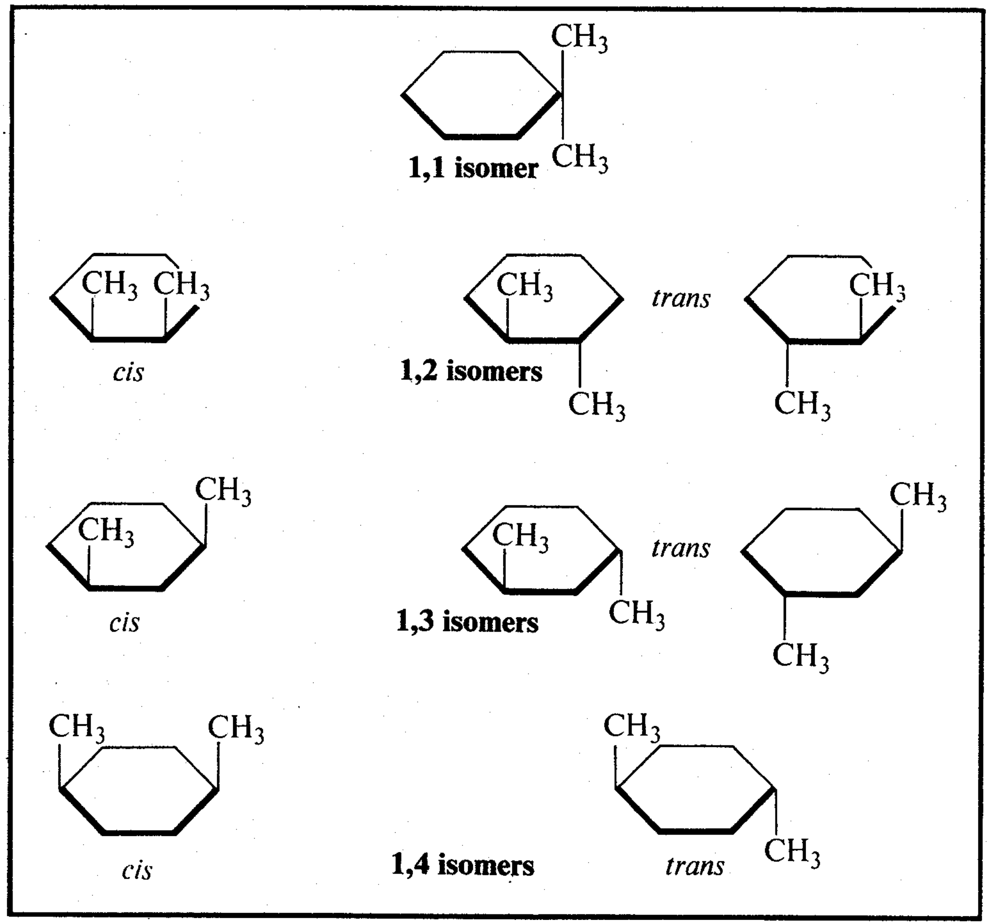


Fig. 31 There are seven possible isomers of dimethylcyclohexane if each pair of optical antipodes is considered as a single compound or nine if the optical antipodes are included. To determine the number of isomers the cyclohexane ring may be assumed to be a planar hexagon.

requires much energy) and at room temperature is extremely slow. The two isomers are thus stable and can be separated.

The stability of such isomers, however, is not always so high: *cis, trans*-sorbic acid isomerizes quite easily into the *trans, trans* isomer. In the presence of certain catalysts, e.g., palladium, *cis* and *trans*-butene interconvert until they reach an equilibrium composition (Fig. 30).

This type of stereoisomerism, also called geometrical isomerism, is not confined to compounds with double bonds. Cyclic compounds provide further examples. There are seven compounds whose formulae correspond to that of dimethylcyclohexane (ignoring the presence of optical antipodes). The structures can be assigned in the following way: one is assigned to 1,1-dimethylcyclohexane, and two each to the 1,2 isomer, the 1,3 isomer and the 1,4 isomer. Without introducing further complications (we shall discuss these later) and supposing that cyclohexane has a planar structure, we can assign to one of the compounds of each pair of isomers a *cis* structure and to the other a *trans* structure (Fig. 31).

A further case of stereoisomerism arises from the tetrahedral character of the carbon atom, a structure which, as we know, is at the base of the phenomenon of optical activity. As we have already noted, certain compounds exist in enantiomorphic forms which are related to each other as a right hand is to a left. These enantiomorphic forms are isomers and have identical properties except for the sign of their optical activity. They are defined as dextro or laevo isomers (or enantiomorphs or optical antipodes) and are shown with the signs (+) and (−) and with the letters D and L or *R* and *S* (for nomenclature see Appendix II, p. 239).

Any compound with a dissymmetric structure obtained in the laboratory by conventional methods is, in fact, a mixture of two optical antipodes. This must be remembered when considering the number of isomers of a given structure. Thus, because of optical isomerism, there are 11 isomers of heptane and not 9 (see p. 66) because two of these consist of pairs of optical antipodes; there are 9 and not 7 for dimethylcyclohexane since 1,2 and 1,3-*trans*-dimethylcyclohexane exist in enantiomorphic forms.

If there are two or more centres of stereoisomerism in a molecule, there is a further possibility; that of diastereoisomerism which was mentioned in chapter I and which is due to the different combinations obtainable with such successive centres, for example, DDD, DDL, DLD, etc. To be precise there is no conceptual difference between the diastereoisomerism of the tartaric acids and the geometrical isomerism of the *cis*- and *trans*-2-butenes and in many modern texts they are treated in the same way.

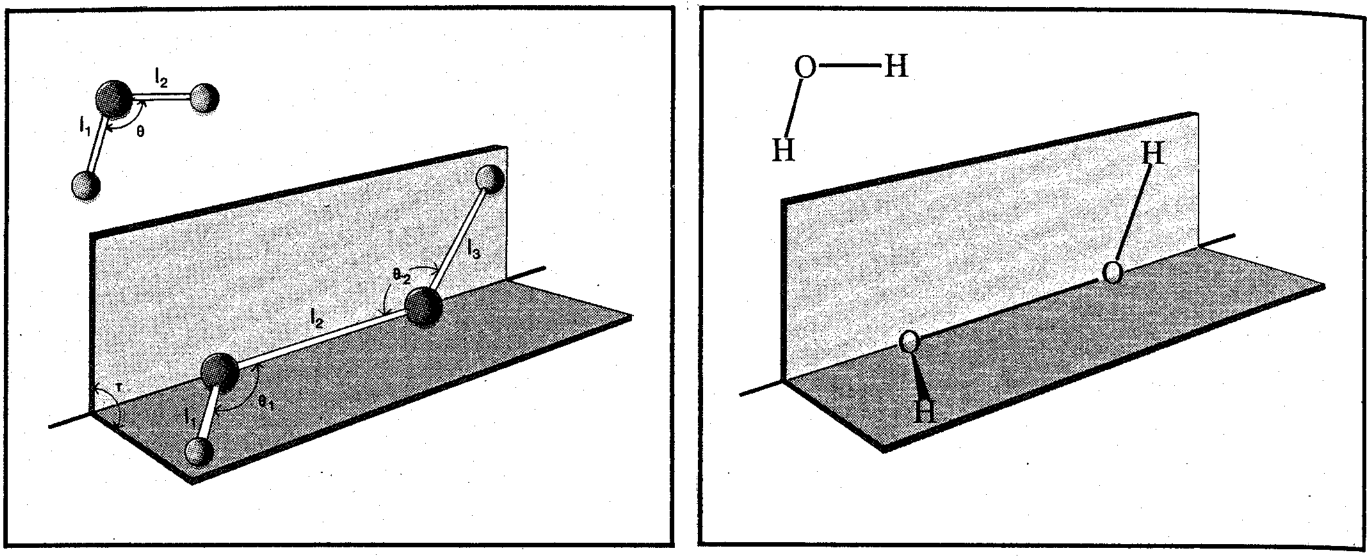


Fig. 32 On the left, geometrical parameters for a system of three and four points which are not co-planar. On the right, the structures of water, H_2O, and hydrogen peroxide, H_2O_2. The latter is the simplest molecule on which conformational analysis can be performed. The dihedral angle in the stable conformation of hydrogen peroxide is about 90°.

Conformational analysis

In the preceding pages we have taken several steps towards understanding the shapes of molecules. We have seen that for a certain empirical formula there may be different structural isomers, positional isomers, geometrical isomers and optical isomers. We have observed that the arrangement of the atoms in a molecule can be expressed in terms of the bond lengths and valence angles. But in addition to the quantities we have cited there is a third structural parameter whose influence will now be discussed in greater detail. This parameter is internal rotation around the bonds.

From a geometrical point of view, a set of three points, in our case three atoms, is completely defined when two distances and an angle are known. If, however, we consider a set of four points, we find that it is not sufficient just to know one more length and one more angle to determine unambiguously the relative positions of the atoms. Four points do not necessarily lie in the same plane. One of the ways of describing their positions is by considering the angle formed by the plane on which the first three points lie and that formed from the last three (Fig. 32). The angle formed by the two planes is called the dihedral angle and its value, together with those of three lengths and two angles, exactly defines the geometry of the system.

The simplest structure of this type is that of hydrogen peroxide, H_2O_2. The four atoms are neither co-linear nor co-planar. The shape of this molecule is defined by two O—H distances (both equal), the O—O distance, the two H—O—O angles (both equal) and a dihedral angle around the O—O bond. The variation of the dihedral angle can be viewed as a rotation of the hydrogen atoms, or of the O—H bonds, around the O—O bond.

This geometrical introduction takes us to the heart of conformational analysis, the most subtle and detailed aspect of modern stereochemistry. In order to simplify the discussion, we shall try to use molecular models and the symbolic notation which originate from the models. Within limits, molecules can be represented by rigid, or almost rigid, mechanical models: the atoms as spheres with given diameters and the bonds by rods of an appropriate length. We are obviously dealing with simplified representations; it is known, in fact, that atoms are not fixed but vibrate about equilibrium positions and thus their valence angles and bond lengths are of average values rather than instantaneous ones. We have also seen that the volume occupied by the atoms and groups cannot be determined in a rigorous manner and that they cannot be considered simply as hard, rigid spheres. However, even with these limitations, the use of models

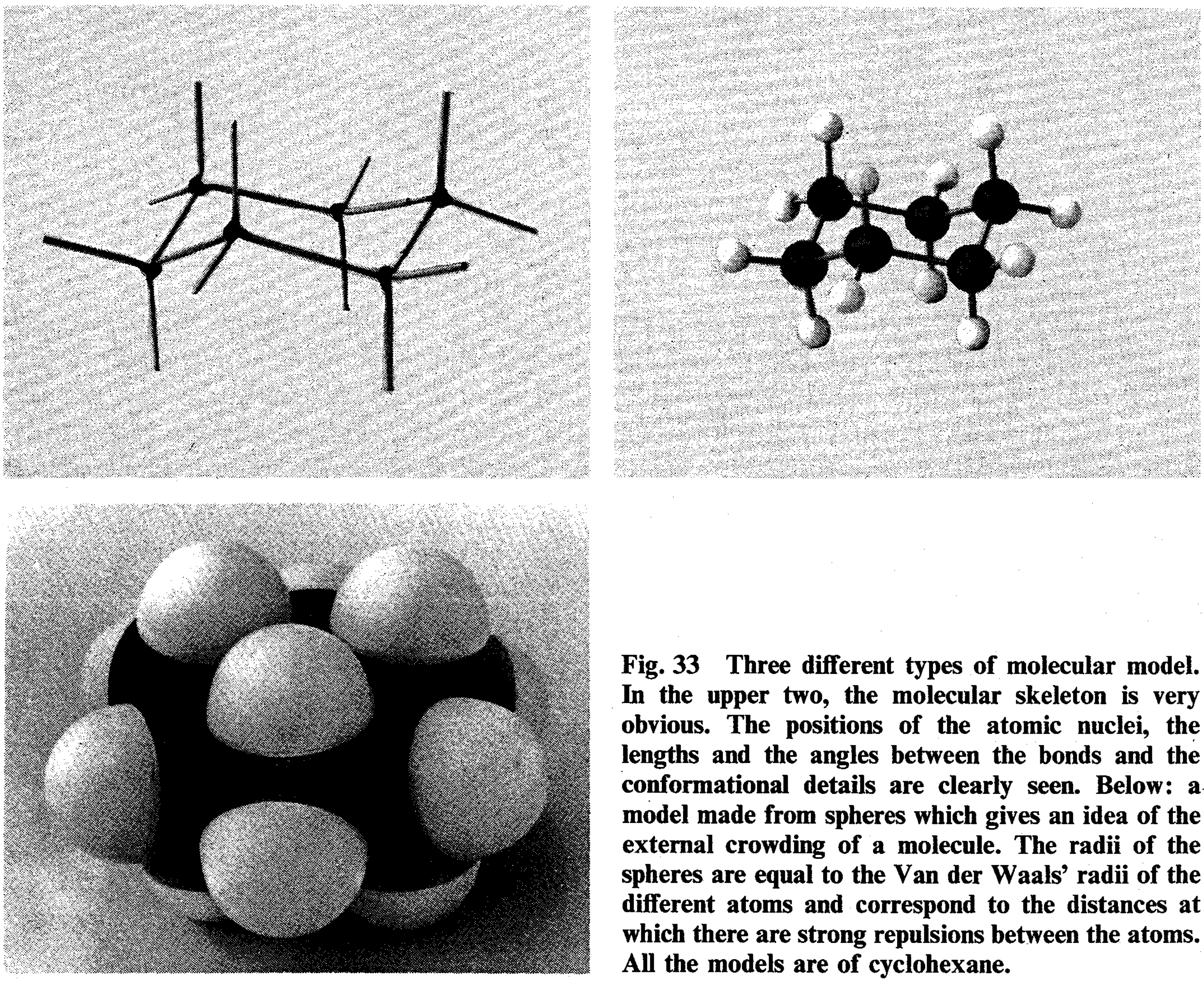


Fig. 33 Three different types of molecular model. In the upper two, the molecular skeleton is very obvious. The positions of the atomic nuclei, the lengths and the angles between the bonds and the conformational details are clearly seen. Below: a model made from spheres which gives an idea of the external crowding of a molecule. The radii of the spheres are equal to the Van der Waals' radii of the different atoms and correspond to the distances at which there are strong repulsions between the atoms. All the models are of cyclohexane.

is continually growing because of the difficulty of efficiently representing three-dimensional structures in two dimensions.

Two fundamental types of models are widely used by chemists: those which demonstrate the skeletal structure of the molecule and those which show better its shape and external dimensions (Fig. 33). Both have merits and faults and in a certain sense are complementary to each other. For our immediate purpose, the fundamentals of conformational analysis, the first type is to be preferred.

Now we come to the problem of ethane, the keystone of modern stereochemistry. The molecule of ethane, C_2H_6, is formed from two carbon atoms, each bonded in a tetrahedral arrangement to three hydrogen atoms and another carbon. If we consider for a moment only two hydrogen atoms, one on each carbon atom, we have an analogous situation to that of hydrogen peroxide. The four atoms H, C, C, H are not co-linear and to define their positions it is necessary to know the dihedral angle around the C—C bond. This is a geometrical consideration. In physical terms, however, we must ask ourselves whether it is reasonable to speak of fixed positions of the hydrogen atoms or whether we should rather speak of free rotation of the two -CH_3 groups with respect to each other.

This last problem cannot be resolved without considering the time interval during which the observation is made. For a relatively long interval (e.g., 0·001 seconds), the idea of a rapidly rotating top can be sufficient for most purposes; but if the period of observation falls to between 10^{-7} and 10^{-9} seconds (this can be achieved using rotational and vibrational spectroscopy), the hypothesis of free rotation is totally inadequate.

A study of the spectroscopic and thermodynamic properties of ethane has led to the conclusion that the two methyl groups are neither fixed nor do they freely rotate. The importance of this fact was clearly appreciated in the 1930s by various groups, especially those of Kenneth S. Pitzer in America and San-Ichiro Mizushima in Japan. In rotation around the central bond, the methyl group experiences resistance, like a ball rolling over uneven ground. We shall therefore speak of valleys and hills or, better, of minima and maxima of energy, and of barriers to rotation. It was possible to establish that the maximum of energy coincided with the form in which the hydrogen atoms of the two methyl groups are closest to each other (angle of rotation 0°) and the minima with that in which they are as far apart as possible (angle of rotation 60°). Owing to the identity of the six hydrogen atoms, the maximum height of the barrier is repeated three times in a complete rotation (at 120°, 240° and 360°) and there are also three energy minima (at 60°, 180° and 300°).

A representation of molecular models of ethane, two different

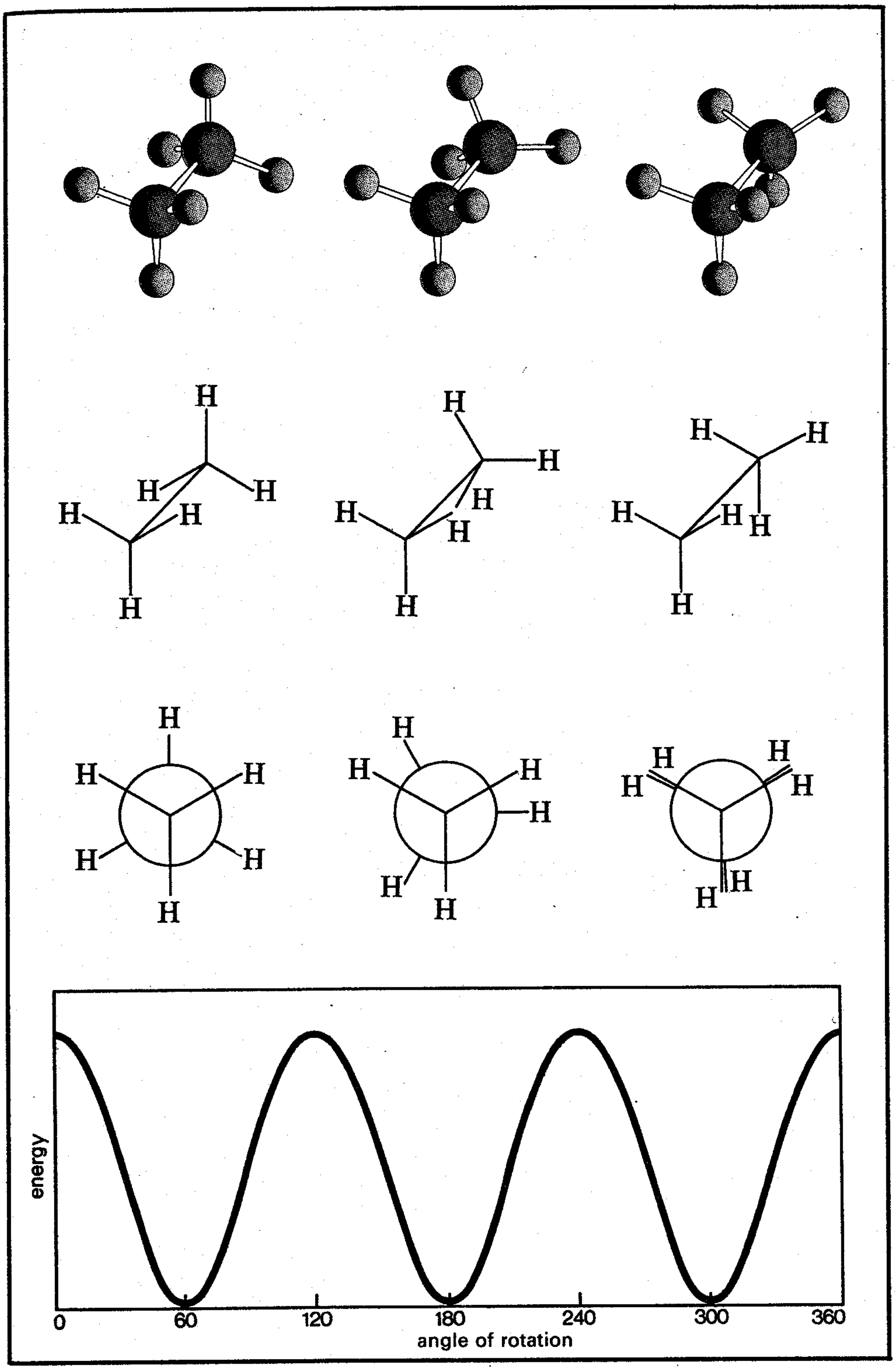


Fig. 34 Molecular models, formulae in perspective and Newman projections for three conformers of the ethane molecule CH_3–CH_3. The Newman projections are obtained by looking at the molecule along the bond around which rotation occurs. The carbon atom at the back is indicated by a circle and the one at the front by a point. The three remaining valences are arranged at 120° to each other. The conformation on the left is staggered (with dihedral angles of 60°, 180° and 300°), a general conformation is shown in the centre and an eclipsed (with dihedral angles of 120°, 240° and 360°) conformation on the right. The potential energy of the molecule as a function of the dihedral angle is shown below. The energy minima occur at 60°, 180° and 300°, corresponding to staggered conformations which are thus more stable. The height of the potential barrier is about 3 Kcals per mole.

types of planar projection and the curve of the potential energy are shown in Fig. 34.

Each form of ethane obtained by rotation around the C—C bond is called a *conformation;* the most stable conformations of minimum energy are called *conformers.* Conformations with the hydrogen atoms of the two methyl groups at their closest positions (angles of rotation 120°, 240° or 360°) are said to be *eclipsed* while those with angles of rotation 60°, 180° or 300° are said to be *staggered.*

The height of the potential barrier to internal rotation was found by measurement to be 3 Kcals per mole; it is sufficiently small to be easily overcome at room temperature but large enough for its effects to be observable at a molecular level. If, by using a very short exposure, it were possible to photograph an ethane molecule, it would appear frozen in the staggered conformation; if, however, the photo were taken with a much longer exposure, it would look like a spinning top.

After this description of ethane, we can go on to see how more complex molecules will behave. The change from ethane to propane does not require any modification of the picture; the low energy conformation is staggered and the barrier is only a little higher. On the other hand a new phenomenon arises when *normal*-butane, C_4H_{10}, is considered.

If we took one hundred photographs of a butane molecule with our extremely fast camera (assuming that the photographic studio is at a normal temperature, at 25°C), we would not find one hundred identical photographs as we did for ethane: 70 would be of one type, 15 of another and the final 15 of a third type. This shows that there are three stable forms in which the butane molecule can exist for finite intervals of time. With the aid of models, let us now try to identify these forms.

Butane consists of a chain of four carbon atoms CH_3-CH_2-CH_2 -CH_3. A non-planar arrangement of atoms as in hydrogen peroxide can now occur not only for the hydrogen atoms but also for the carbon atoms. Ignoring the hydrogen atoms for simplicity, let us try rotating one end of the molecule around its central bond. Starting from the conformation in which the terminal carbon atoms are eclipsed (that is to say they appear superimposed when viewed along the central C—C bond), we see that the energy of the system diminishes (and thus the stability increases) up to an angle of 60°, then grows to 120°, falls again to a still deeper minimum at 180°, rises in a symmetrical manner up to 240°, falls again to 300° and finally rises to the starting value after the complete rotation (Fig. 35). There are thus again three minima and three maxima but these are not all equal. The most stable position (that found in 70 of the photographs) is the conformation at 180° which is given the name

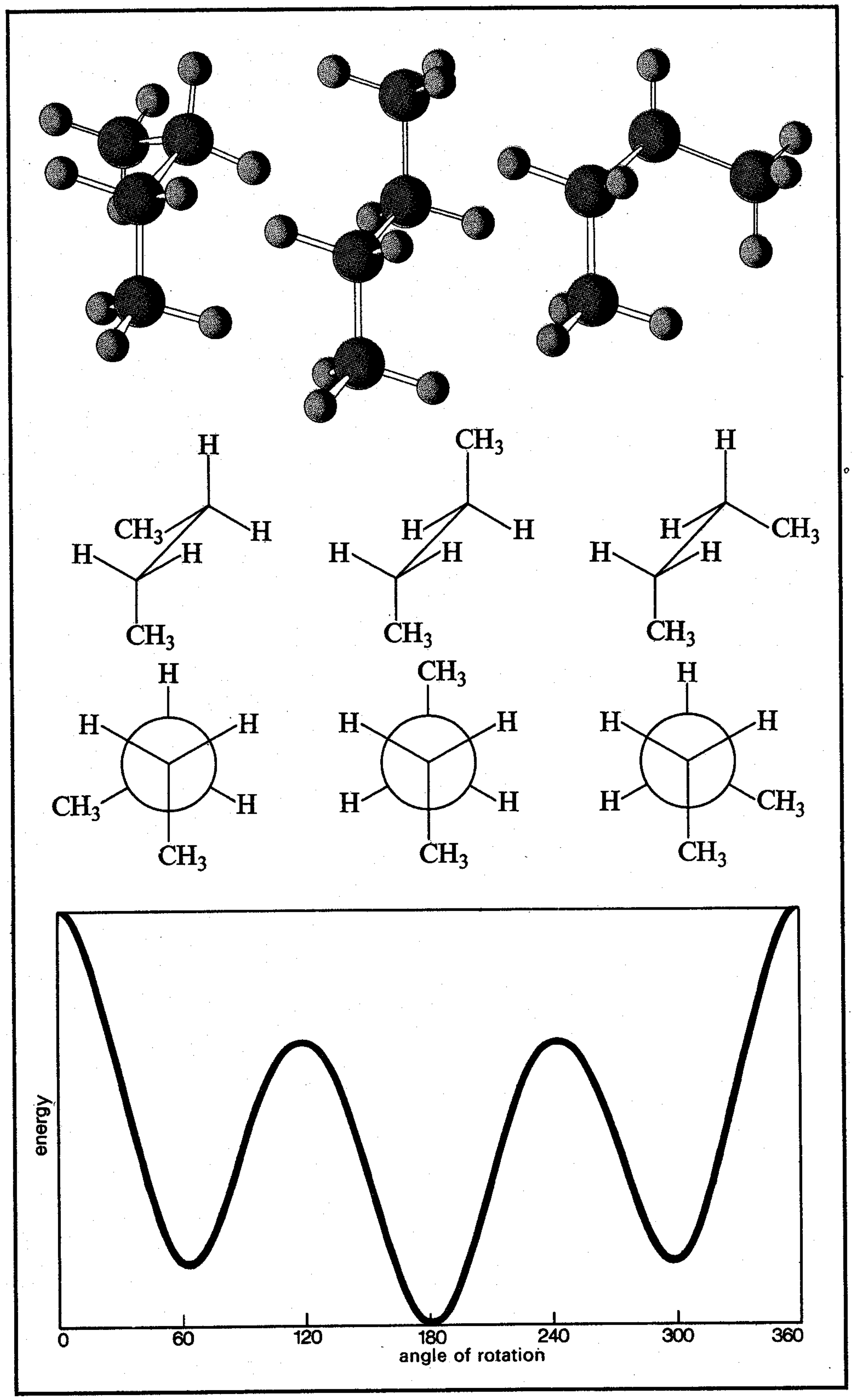


Fig. 35 Molecular models, formulae in perspective and Newman projections for three staggered conformations of *normal*-butane. C_4H_{10}. From the left, the *gauche* form (at 60 °), the *trans* (or *anti*) form (at 180°) and a second *gauche* form (at 300°), a mirror image which cannot be superimposed on the first. The most stable form, as the energy profile shows, is the *trans*; but the *gauche* forms also exist to the extent of about 30 per cent of the total molecular population at room temperature, and their concentration increases as the temperature rises.

trans or more correctly *anti*; but there are also another two positions, although less populated than the first, at 60° and 300°. One can easily see that these two positions are mirror images of each other; consequently, they possess equal energy and thus have an equal probability of existence (fifteen photographs for each). The name *gauche* or *skew* is given to these forms.

The forms are shown in Fig. 35 in perspective and Newman projection along with an approximate curve of the potential energy as a function of the angle of rotation. The difference in energy between the *trans* form and the two *gauche* forms is about 0·8 Kcals per mole, a value which corresponds to an approximate relationship of 70 : 15 : 15 for the respective probabilities of existence at room temperature.

The calculation of conformational energy and the shapes of more complex molecules

Before proceeding to examine other molecules, we should investigate the physical origins of these phenomena of potential barriers and energy minima. Unfortunately, we must confess our ignorance at the present stage of chemical knowledge. Very little or nothing is known about the origin of barriers and whether they arise from the electronic properties of bonds or from repulsion between atoms. Also very little is known about methods with which the relative energies of different conformations may be calculated. This is a field of much discussion for various schools of theoretical chemistry. A logically rigorous solution, derived from the same quantum-mechanical principles on which all structural chemistry is based, has been developed only recently and is still limited to very simple molecules. However, an attempt has been made to resolve the problem in an approximate way, rather unsatisfactory from the theoretical point of view but quite productive in practice.

This method is directly associated with the mechanical model described earlier in which the atoms are represented as more or less deformable spheres and the bonds as rods or, better, as stiff springs. Conformational energy is generally separated into four terms, the first arising from the deformation of the average length of bonds and the second from the distortions of the valence angles with respect to their normal values. The third refers to the torsional strain, also called Pitzer strain, arising from the potential barrier to internal rotation around the bonds, which we discussed with regard to ethane (Fig. 34). Finally, the fourth term is related to the interactions between neighbouring, but non-bonded, atoms and is often called Van der Waals energy. For this term also we can give a mechanical analogy. Two balloons tied to a thread and suspended from the same support are in contact with each other; being in a condition of equilibrium, their energy is the minimum compatible with the bonds of the system. If we now try to press the two balloons together, we must apply a certain force which causes the energy content of the system to rise. When the force is removed the balloons lose their acquired energy and return to their equilibrium positions.

Analogously, when two, non-directly bonded atomic nuclei are rather far apart (more than 0·40–0·50 nm) they mutually attract each other, though rather weakly. However, at less than a certain equilibrium distance, characteristic for each pair of atoms, a further approach requires a large increase of energy, inversely proportional to the twelfth power of the distance between the nuclei. The energy of the system rises to prohibitive levels for an approach closer than 0·05–0·10 nm beyond the equilibrium position. If the two atoms in question belong to the same molecule and are connected through three or more bonds, they will show a strong tendency to move apart from each other. Conformations which have strong Van der Waal's interactions are not generally stable; if the molecular structure allows it, the atoms will rotate around the bonds until they reach other positions of lower energy (Fig. 36).

Sometimes two or more energetic factors arise in direct opposition. A typical case is that of 'iso-octane' (2,2,4-trimethylpentane) a compound with which all motorists are familiar*. *Iso*-octane is a highly branched molecule whose staggered conformations have interatomic distances, between the hydrogens of the methyl groups, which are very small and, consequently, have very high Van der Waals energies. On the other hand, the eclipsed conformation (unfavoured with respect to Pitzer energy) allows a separation of the atoms and constitutes in reality the more stable conformation (Fig. 36).

In other cases molecular structure is not compatible with the existence of low energy conformations and the molecule tends to lower the repulsion between the atoms by deformation of other geometrical parameters. The valence angles are the most easily deformed (Fig. 36). The more one takes account of the different types of deformation which the molecule can undergo, the lower the calculated energy becomes for the molecule and the nearer it approaches the experimental value. In determining the most stable shape of a particular molecule, a compromise has to be reached

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* *Iso*-octane is, in fact, the hydrocarbon on which the petrol anti-knock scale was based. By definition, a petrol with an octane number of 100 has an anti-knock power equal to that of iso-octane, while an octane number of 80 corresponds to the anti-knock power of a mixture of 80 parts of *iso*-octane and 20 parts of *normal*-heptane.

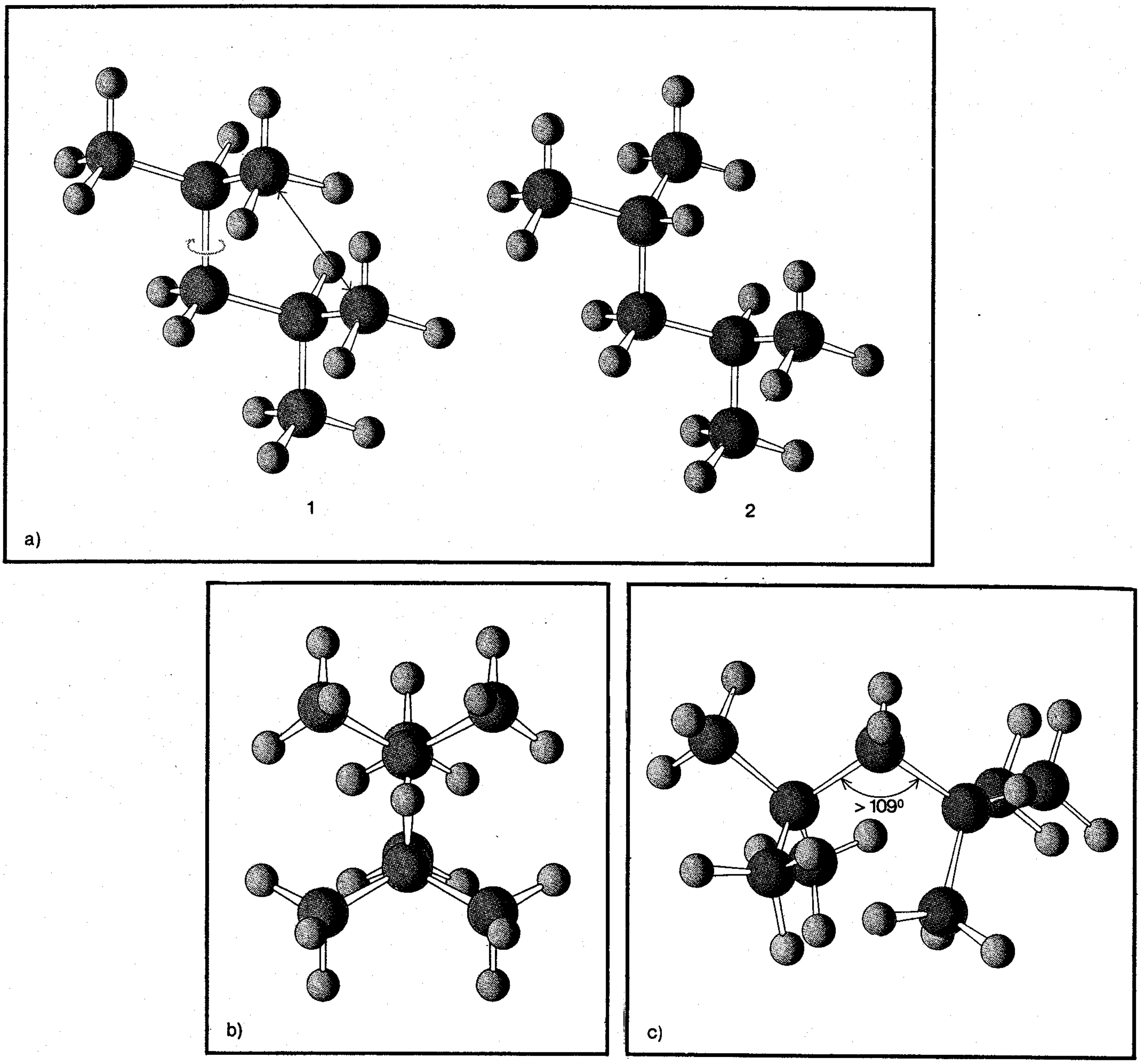


Fig. 36 The interaction between the non-bonded atoms, or Van der Waals interaction, of the two methyl groups arranged as indicated in the formula *a*1 causes the energy of the 2,4-dimethylpentane molecule to be too high. By internal rotation around one bond the molecule is converted into the more stable form *a*2. For 2,2,4-trimethylpentane, i.e., *iso*-octane, there is no staggered conformation with low energy. The most stable conformation is the one with the two methyl groups eclipsed with respect to the two central hydrogen atoms (*b*). In 2,2,4,4-tetramethylpentane the presence of a further methyl group gives rise to considerable strain in the molecule. A suitable deformation of the valence angle causes the two quaternary carbon atoms to move slightly away from each other (*c*).

between the various factors which can cause notable deviation from the values for bond lengths, angles etc., generally accepted as typical. It is on this point that many pictures based on models reach a stumbling-block. One must always remember that the average values with which the models are built, precisely because they are averages, do not necessarily correspond to those of a particular case.

A further consideration concerns the simultaneous presence of molecules in different conformations. At this point, it is necessary to recall briefly the properties of the various states of matter. The gas, liquid and crystalline states are different essentially because of differences in the freedom of movement of the molecules with respect to each other. They are rigorously fixed in crystals, free to move throughout a limited volume in a liquid and throughout all the space available to a gas. But there are other differences concerned with the freedom of internal motion of molecules. In general, freedom of internal rotation is prohibited in crystals and all the molecules have the same shape which usually coincides with the most stable form, although this may be slightly deformed because of interaction with neighbouring molecules. On the other hand, molecules in the gas or liquid state have great mobility and, having sufficient energy to overcome the barrier to internal rotation, can assume a multiplicity of shapes.

Reverting to the case of butane, even if the *trans* form is more stable than the *gauche*, a system of many molecules (one gram of butane contains about 10^{22} molecules) reaches its maximum stability at room temperature with an average composition of 70 per cent *trans* molecules and 30 per cent *gauche*.

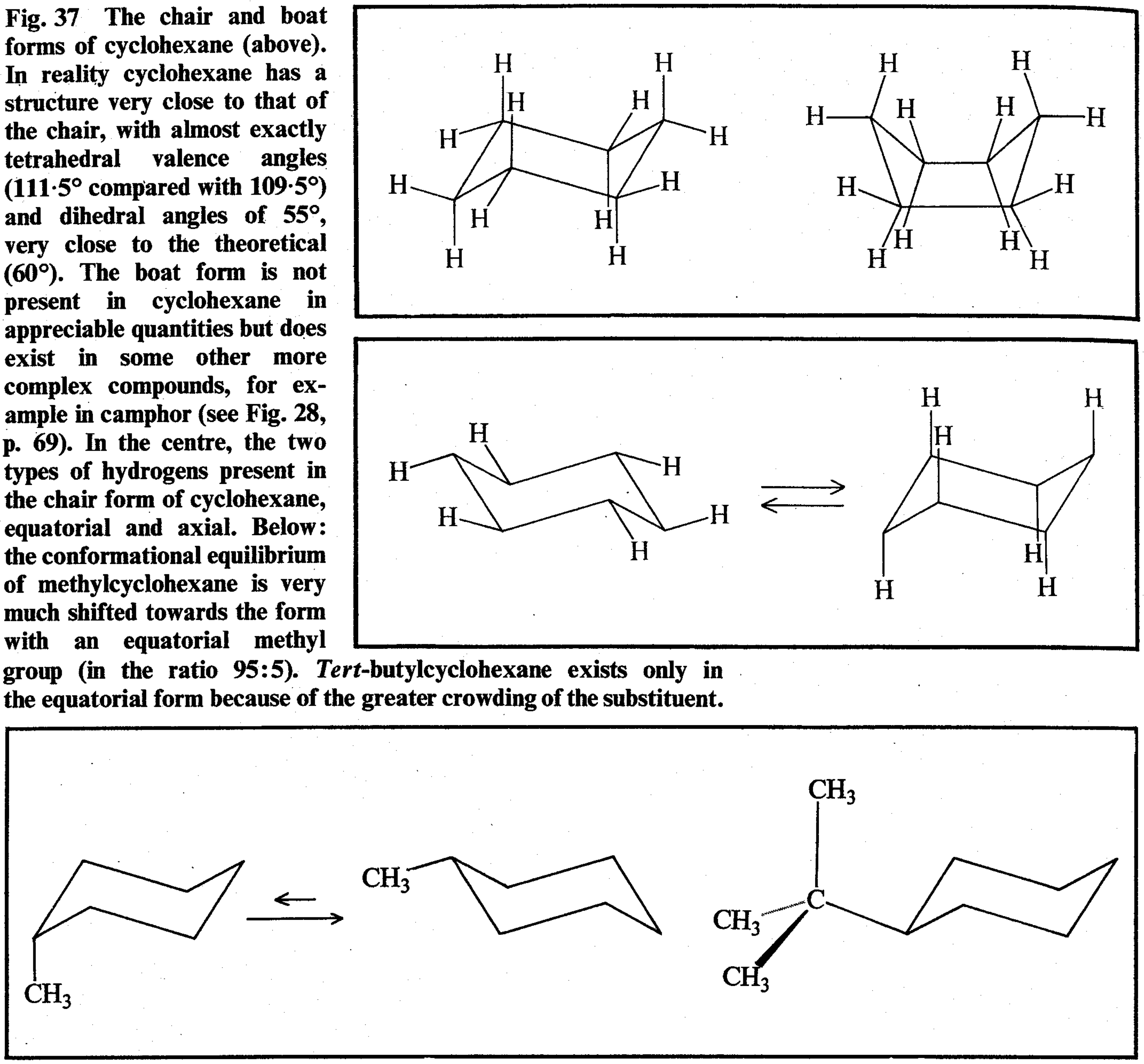
At absolute zero (−273°C) butane exists only in the *trans* form but at a higher temperature a certain disorder is established in the system, which increases with the rise in temperature. Paradoxically, this disorder, which requires the passage of a certain number of molecules from the *trans* to the higher energy *gauche* form, lowers the free energy of the system and makes it more stable.

Cyclohexane and cyclic compounds

If cyclic compounds lie at the centre of a large part of chemical research, we can certainly say that they almost completely dominate the field of conformational analysis. It is here that modern stereochemistry has achieved its outstanding success. Cyclohexane, as the fundamental compound of this series and as the model for the most complex of natural products, was the experimental and theoretical testing ground. Sugars, terpenes and steroids are the areas in which the use of such a method has been most useful for analyzing structures, understanding their reactivities and predicting their behaviour.

Modern stereochemistry has led to a great revival in the principles of Sachse which had long been misunderstood and forgotten. Contrary to the theory of Baeyer which then prevailed, Sachse predicted two possible non-planar forms of cyclohexane: the chair and the boat. This hypothesis has now been confirmed, at least for

Fig. 37 The chair and boat forms of cyclohexane (above). In reality cyclohexane has a structure very close to that of the chair, with almost exactly tetrahedral valence angles (111·5° compared with 109·5°) and dihedral angles of 55°, very close to the theoretical (60°). The boat form is not present in cyclohexane in appreciable quantities but does exist in some other more complex compounds, for example in camphor (see Fig. 28, p. 69). In the centre, the two types of hydrogens present in the chair form of cyclohexane, equatorial and axial. Below: the conformational equilibrium of methylcyclohexane is very much shifted towards the form with an equatorial methyl group (in the ratio 95:5). *Tert*-butylcyclohexane exists only in the equatorial form because of the greater crowding of the substituent.



the chair form. After Hückel succeeded in isolating two decahydronaphthalenes (Baeyer's theory predicted only one of them), there could no longer be any doubts; but another twenty years were required before the structure of cyclohexane could be definitely proved.

Due particularly to studies by Hassel, we now know that the chair form of cyclohexane is effectively the stable form. It is completely unstrained, the valence angles are very close to the theoretical values, the hydrogen positions on adjacent carbon atoms are staggered with respect to each other and there are no appreciable Van der Waals interactions between non-directly bonded atoms. This cannot be said for the boat form which has four pairs of eclipsed hydrogen atoms and a strong Van der Waals' interaction between some of the hydrogen atoms. The energy of this form is about 5 Kcals per mole higher than that of the chair and the boat form is thus found only to an extremely small extent at room temperature. An examination of the chair reveals other interesting characteristics. The most important of these is that there are two chair forms which can transform into each other by means of rotation around the bonds. In contrast to the situation with the three conformations of butane (*trans,* dextro *gauche* and laevo *gauche*) these two forms are absolutely indistinguishable. However, the exchange between them is extremely important, as we shall soon see.

In cyclohexane one can distinguish two series of hydrogen atoms depending on their different positions with respect to the average plane of the molecule. Six hydrogen atoms are close to this plane while the other six have the carbon-hydrogen bonds directed perpendicularly to the molecular plane so that three are above and three below this plane. The six atoms of the first series are called *equatorial* and the six of the second *axial.* Their properties should be different but, because of the rapid interconversion of the two chair forms, the axial and equatorial hydrogens continually exchange positions. If it were possible to observe cyclohexane with some relatively slow method (a camera at one-hundredth of a second) we would see only one type of hydrogen atom whilst with a more rapid method (or at lower temperatures when the exchange rate is less) the axial and equatorial series could be clearly distinguished. This is really the reason why Sachse's theory was not taken up. Chemists were not accustomed to thinking in instantaneous terms; they lacked the rapid experimental methods required to see these details which are totally beyond the scope of the methods of chemical investigation of Sachse's day.

Let us examine this matter in more detail. If the axial and equatorial positions are equally probable for the hydrogen atoms of cyclohexane, they are not equally probable, at least in principle, when a hydrogen atom is replaced by another atom (for example bromine) or by another group of atoms (for example a methyl group -CH_3). The two chair forms of methylcyclohexane are no longer identical and they do not have equal energy (Fig. 37); the methyl interacts less with the rest of the molecule when it is in an equatorial position than when it is in the axial position. The first conformation, of lower energy, is thus more abundant and the average composition of methylcyclohexane at room temperature consists of 95 per cent with an equatorial methyl group and only 5 per cent with an axial methyl. Consequently, five of the hydrogen atoms have a 95 per cent probability of being in equatorial positions. The opposite is true for the remaining six hydrogen atoms.

If, instead of the methyl group, we consider a bulkier group (i.e., one capable of interacting to a greater degree with the rest of the molecule) like the *tertiary* butyl group, the axial form has such a high energy that its concentration falls to an extremely low value under normal conditions and the molecule becomes quite rigid. It is thus possible to study the reactivity of certain atoms or functional groups in a selective manner in each of the equatorial and axial positions.

To illustrate these points further, let us now examine the various isomers of dimethylcyclohexane. On page 73 we said that the number of these isomers is 7 (or 9 if the optical antipodes are included). Neglecting the 1,1 isomer, they may be grouped in three pairs of isomers of the *cis-trans* type. In 1920 Von Auwers proposed a rule which was obeyed by nearly all the compounds known at that time. According to this rule, the *trans* isomers should have greater stability, and a lower density and boiling point, than the corresponding *cis* isomer. A *cis* and *trans* structure was assigned to two 1,3-dimethylcyclohexanes on this basis. Some years later Mousseron showed that this assignment was incorrect by resolving the compound previously assumed to be *cis* (only the *trans* isomer should be resolvable; see Fig. 31, p. 72).

Conformational analysis took care of this apparent anomaly in a very simple way. The Von Auwers' rule was not to be associated with the *cis-trans* structure but with the presence of substituents in the axial or equatorial positions. This is the structural detail which determines the energy and volume of the molecule and influences the other properties. The most stable form of each isomer is shown in Fig. 38. Among the dimethyl-cyclohexane isomers the 1,2-*trans*-1,3-*cis*-and 1,4-*trans*- have two equatorial substituents while the 1,2-*cis*-, 1,3-*trans*- and 1,4-*cis*- have one axial in complete agreement with the modified rule.

The conformations of natural products

When in 1950 Derek Barton announced for the first time the principles of conformational analysis of steroids the ground was ready to receive them. Taken in isolation and applied to the simplest compounds those principles were already known, at least to the more advanced research groups. However, Barton's work was of catalytic importance. Taking more or less abstract notions he had transformed them into an important tool of investigation. For this reason Barton, together with Hassel, was awarded the Nobel prize for chemistry in 1969, a testimony to the immediacy of the topic we are discussing.

The steroids represent a vast class of natural products which are of basic importance for life. Among them, for example, are both male and female sex hormones, ergosterol (from which vitamin D, the

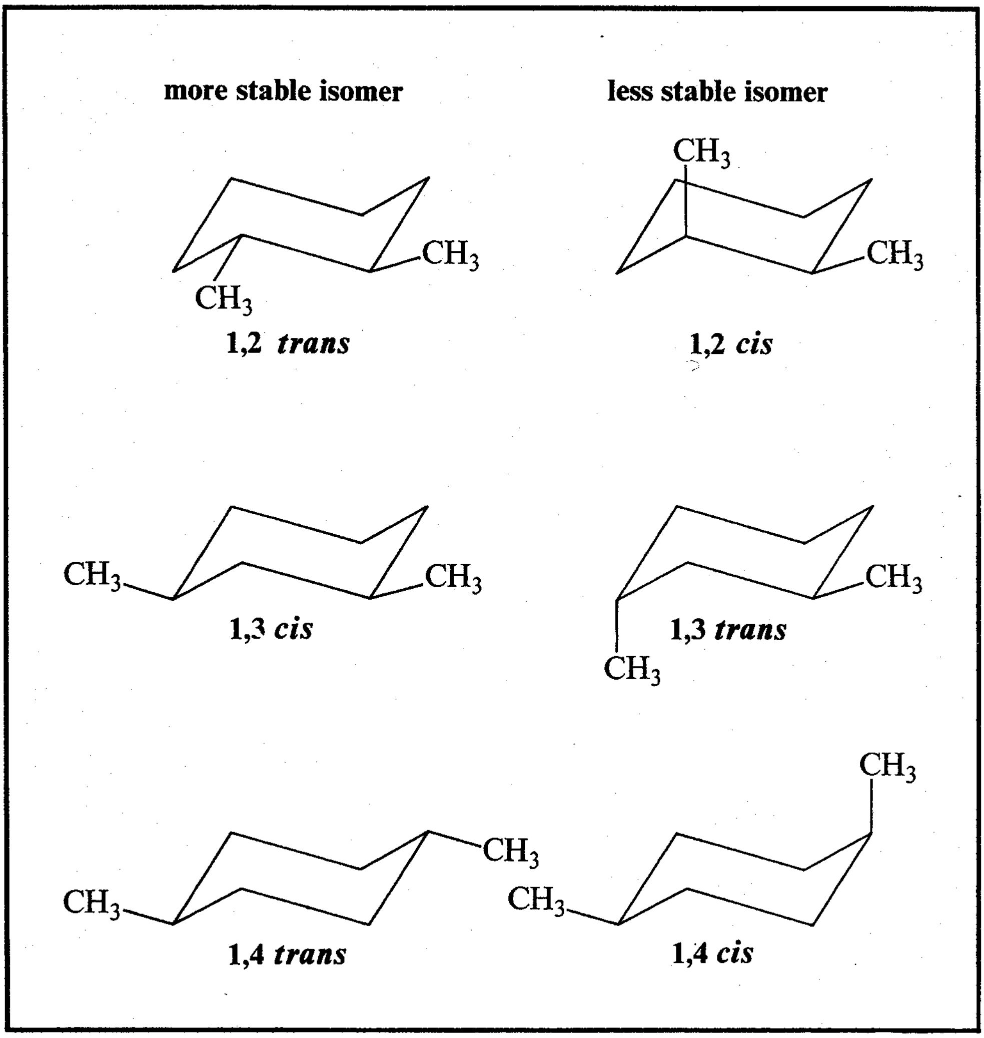


Fig. 38 Conformations of *cis* and *trans* dimethylcyclohexanes (c.f. Fig. 31, p. 72). The isomers with both methyl groups in equatorial positions are more stable than those with one equatorial and one axial substituent. Examination of the configurations shows that the *trans* isomers of 1,2 and 1,4 disubstituted cyclohexanes, and the *cis* isomer for the 1,3 derivative, are of the first type.

anti-rickets factor, is derived), cortisone and the bile acids, cholesterol (found in gallstones and largely responsible for arteriosclerosis) and the active ingredients of digitalis. It may seem strange that so many different physiological actions arise from compounds which belong to the same very homogeneous structural class. The different actions depend mainly on the presence of different types of reactive groups; but even compounds very similar at a chemical level sometimes produce quite different effects in living organisms. It is thus in the detailed structure that the search must be made and it is here that Barton's hypotheses have opened new paths.

The steroids consist of four condensed rings: three of cyclohexane and one of cyclopentane. The conformation of the rings with six atoms is that of a chair; but the joining of the rings makes the whole structure particularly rigid (Fig. 39). This fact enormously simplifies the stereochemical study because, as we have already seen in the case of *tertiary*-butylcyclohexane, there is no possibility of conversion between the two chair forms. The equatorial and axial positions are thus precisely defined and one can often successfully predict the course of a certain reaction, the influence of substituents, or how the

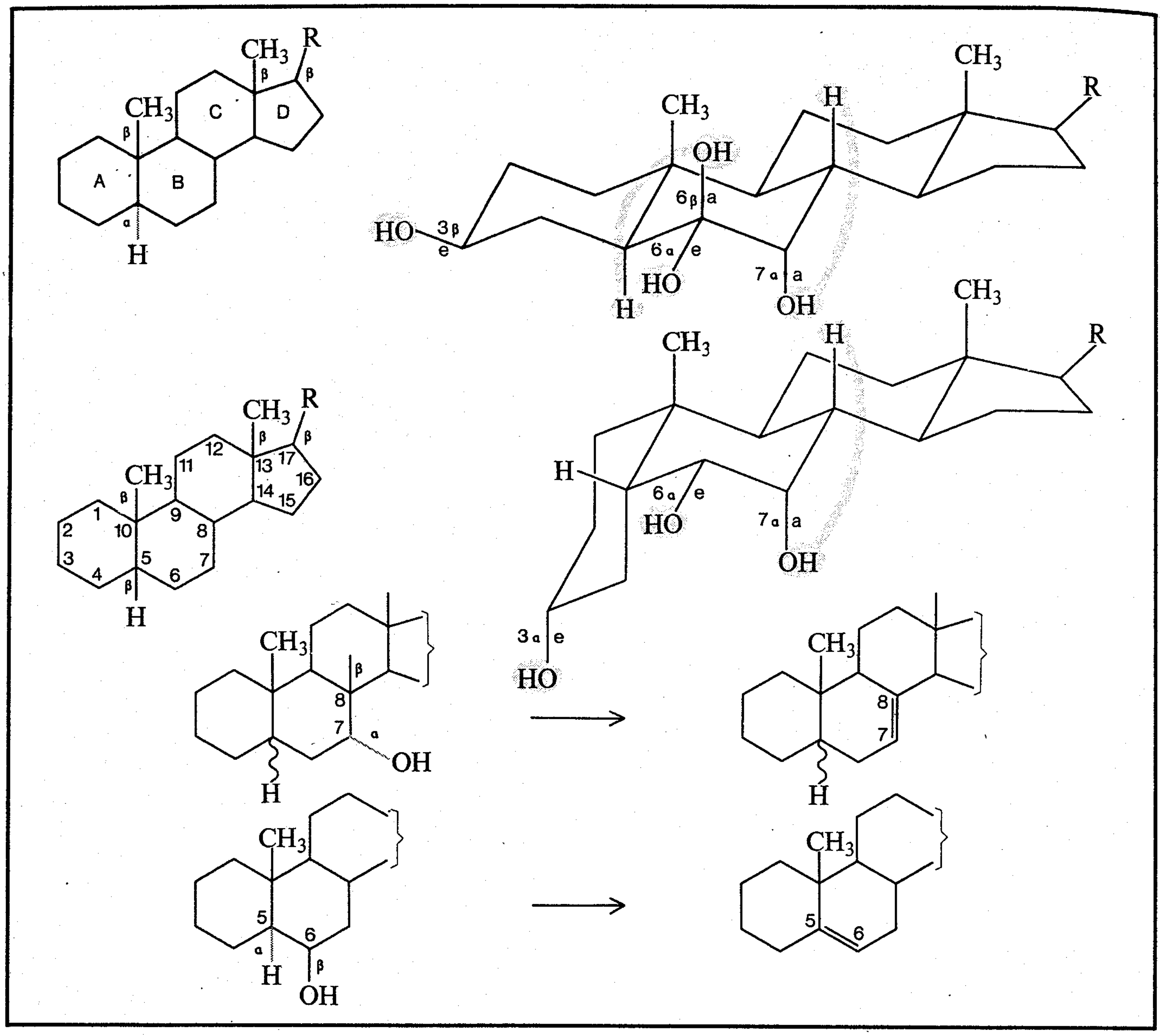


Fig. 39 Planar formulae and conformations of some cholestane (above) and coprostane derivatives. In the planar formulae the bonds in black indicate β substituents and the bonds in grey α ones, while the wavy line signifies that the position of the substituent is not determined or not specified. Conformational analysis gives a simple and rational explanation of many phenomena. The greater stability of equatorial substituents with respect to axial ones, for example, accounts for the fact that 3β- and 6α-hydroxycholestane are more readily formed than the 3α and 6β epimers, while in the coprostane series the favoured compounds are the 3α and 6α. The reactivity of the 7α hydroxyl is similar in the two series while that of the 6α hydroxyl is clearly different. Only in the cholestane series, in fact, is there a planar arrangement (in *anti* conformation) of the hydroxyl and a hydrogen atom which allows the elimination of water and the formation of an alkene (formulae at the bottom).

properties of the compound will be affected by a modification of the chemical structure.

The two fundamental series of saturated steroids are distinguished by a different type of junction between the rings A and B: *trans* in the cholestane series and *cis* in the coprostane series. This fact brings about a different conformation of the A and B rings (which constitute a system analogous to that of the *trans* and *cis* decalins), a different arrangement of the substituents and thus a different reactivity which cannot be accounted for by an examination of planar formulae. We will describe some very significant examples taken from the original work of Barton which was reported in a Swiss journal in 1950 and which is considered by many to represent the birth of conformational analysis.

The most stable configuration for a hydroxyl in position 3 is β in the cholestane series and α in the coprostane,* while in position 6 the α configuration of the hydroxyl is the most stable in both series. An examination of the conformations show us immediately that in the cases mentioned the most stable position is the equatorial, in agreement with our earlier discussion. The inversion of the A/B junction

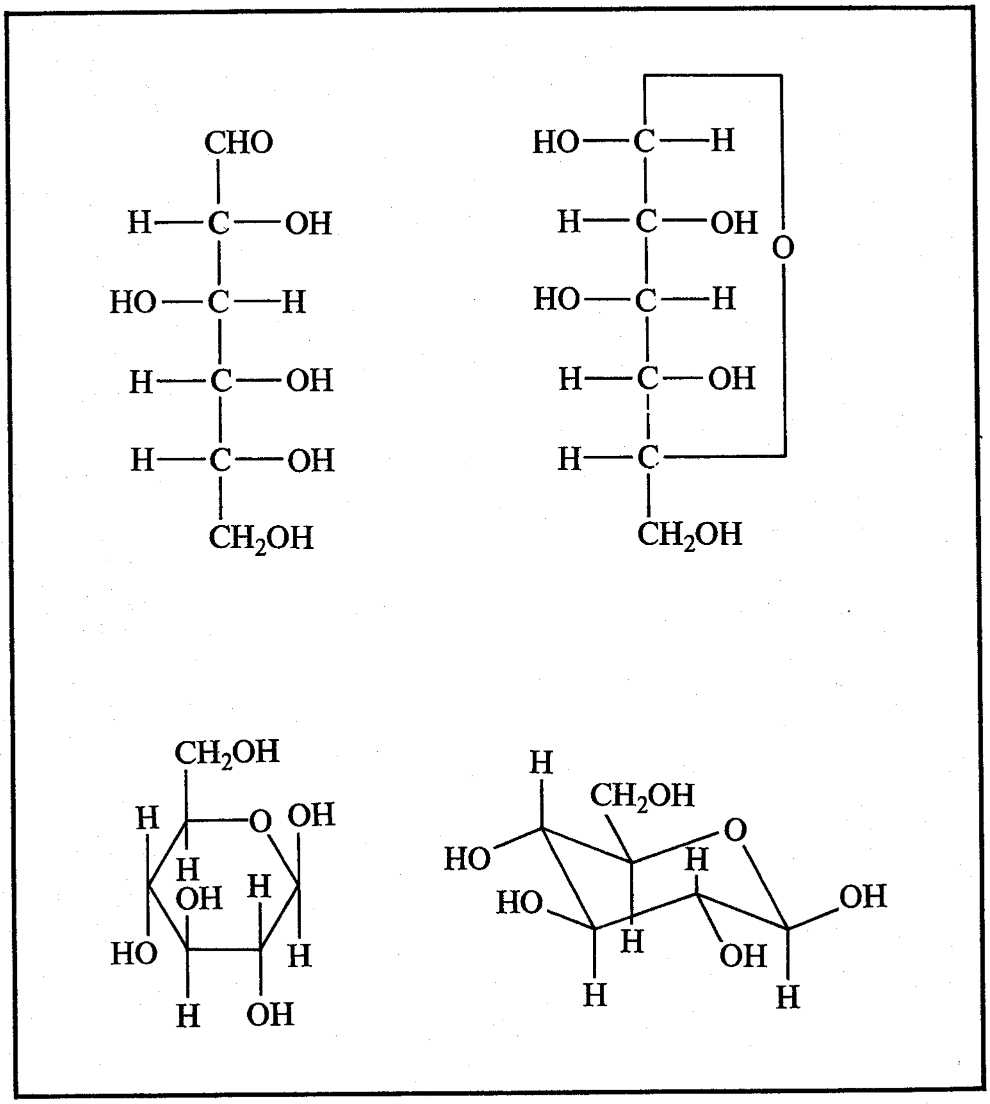


Fig. 40 From the Fischer formula of glucose to the modern representation of the conformation of β-glucopyranose. In this compound all the substituents are equatorial.

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* According to the nomenclature in use for the steroids, substituents are called α when, in the planar formulae drawn as in Fig. 39, they are below the plane of the paper and β when they are above.

in the two series (from *trans* to *cis*) completely changes the order of stability of the A ring but has less influence on the B ring.

Some hydroxylated steroids easily undergo a reaction to eliminate water, producing the corresponding unsaturated compound. Specific conformational effects can be observed in this reaction also, 7-α-cholestanol and 7-α-coprostanol both give the 7,8 olefin but only 6-β-cholestanol dehydrates to give the 5-6 olefin. The steric requirements for ready elimination of water consists in the co-planarity of the four atoms H-C-C-O which must therefore be in a *syn* or, better, an *anti* conformation. This condition is satisfied in the 7-α derivatives of the two series and in the 6-β derivative of the cholestane series alone.

Another class of natural products of which an extensive study was made is the sugars. Strangely enough, from the point of view of modern stereochemistry, cyclohexane and the sugars are closely related.

The reader will recall the extensive work of Emil Fischer in determining the configuration of glucose and the existence of two cyclic forms. The conformational analysis of β-glucose, a constituent of cellulose and thus of a great part of living matter, completely justified Fischer's formula. β-glucose consists of a ring of six atoms and exists in a chair conformation with all the substituents in the equatorial positions (Fig. 40). For this reason it is the most stable of all the sugars (despite the fact that in this particular case dipolar effects make this structure a little less stable than one would predict from purely conformational arguments). The apparent disorder that is seen in the Fischer formula is a crude representation of a more profound rationality. Given its notable stability, it is quite clear precisely why this sugar is the organic compound most commonly found on earth.

IV

Molecular symmetry

Any experimental science struggles continuously between two opposing and contradictory interests. On one side are the search for the unification of knowledge and a universal explanation of phenomena. On the other side are the extension of knowledge, the analytical description of new facts and the application of theories to particular cases. These two directions, the one synthetic and the other descriptive and analytical, are present in all serious research. The equilibrium point depends on many circumstances: the field of study, the means available and, not least, the temperament and ability of the researchers.

Chemistry is a relatively young science and presents widely different aspects. Every year new fields of research are opened and those already existing are explored more widely. Thirty years ago the chemistry of fluorine compounds was practically non-existent; today there are thousands of fluorinated compounds: from Teflon (with which utensiles are covered to facilitate their being cleaned) to missile fuels, from refrigerated gases to special rubbers for the gaskets of coffee machines.

With the discovery of ferrocene in 1951, a new era began in the development of inorganic chemistry; after the discoveries of the nineteenth century and the development of great industrial processes (sulphuric acid, ammonia, non-ferrous metals, etc.), this field of chemistry had been stagnating for many years. In 1962 the first compounds of the noble gases were discovered and today a great many are known.

It is very difficult to bring order and system into a world which is moving so rapidly and it is logical and necessary that the first task of research is to obtain real and accurate experimental data: no real knowledge can be obtained by starting from data which are not sufficiently secure.

Any theory must be verified by experiment. The experimental sciences are different from the mathematical sciences because of this need for external verification. Internal consistency is not enough for a model or theory to be acceptable; there still exists, fortunately, that troublesome, unpleasant event, the result of an experiment. (In truth it could be argued that the experimental verification is not really external but that it is in its own turn tied and conditioned by postulates – both general and particular – of science.)

Yet it is not true that chemists are submerged under experimentation and are not capable of explaining the laws of their science in a unifying manner. The entire field of chemical physics is a testimony to this ability. In this the chemist employs an ever greater mathematical formalism, leaving the laboratory bench and using the computer.

It is said that, in the future, mathematical formulae will replace chemical formulae. These will not only contain information on the structure and physical properties but also the chemical reactivity of compounds. By combining certain equations, it will be possible to know whether the compounds in question will react together, in what manner and at what speed.

We do not wish to pursue this futuristic discourse (results now being obtained, although interesting, do not always support the above prediction) but it seems to us that something similar must be said with regard to the subject in which we are interested. In fact, stereochemistry represents a field in which the formalization of discussion has reached an advanced stage whilst still remaining at a comprehensible level. This judgment concerns a fundamental part of stereochemistry: the prediction of optical activity. We shall now discuss this.

What is symmetry?

Let us return for a moment to the experiments and ideas of Pasteur. The crystals of tartrate which he separated displayed small hemihedral faces orientated in different ways. For that reason the crystals could not be superimposed on each other; one was the mirror image of the other.

If we turn from the crystal to the molecule we have the fundamental condition for predicting the optical activity of a compound. We express it thus: if the compound causes rotation of the plane of polarized light, the mirror image of the molecule cannot be superimposed on the molecule itself. A molecule which has the geometrical form of a hand may therefore be optically active. The mirror image of the right hand is equal to the left hand but it can easily be seen that it cannot be superimposed on the right in the sense that it cannot be made to occupy all and only the space occupied by the right hand.

It will be recalled that, starting from these considerations, van't Hoff proposed the definition of an asymmetric carbon atom, i.e., a carbon atom having four different substituents whose spatial geometry (of a tetrahedral type) cannot be superimposed on its own mirror image. The theory of the asymmetric carbon atom was the misery and delight of organic chemists for almost a century. Although it made an enormous contribution to the explanation of many stereochemical phenomena it placed unnecessary limits on research.

To make this clear we must pose some questions. Can only those compounds with asymmetric carbon atoms be optically active? Are all compounds with asymmetric carbon atoms optically active? The answer to both these questions is 'no'.

The asymmetric carbon atom represents a very important case, the most important of those known in stereochemistry, but it is a particular case. The fact is that van't Hoff's conclusions are still generally accepted but the logical process that lead him to them could nowadays be questioned.

The right course is to examine a structure and its mirror image and determine whether they are identical or not. Van't Hoff rightly followed this course and predicted other types of stereoisomerism, such as that of the allenes, which we shall mention later. If, by and large, chemists are limited to studying the asymmetric carbon atom, it is because compounds which contain it are widely available and are of general interest. A very large number of natural products are optically active and possess one or more asymmetric atoms.

'Asymmetric', 'symmetric' and 'symmetry'; what is the exact significance of these words? From ancient times the artistic shapes created by man have tended to follow more or less obvious rules of repetition and contrast which are often given the name symmetry. This play of symmetry is found not only in visual representations but also in any artistic expression in which the element of rhythm, or the repetition of facts, figures or sounds, dominates.

Poetry, in its formal aspect, is widely influenced by rhythm. The rhythm of the verse, the rhyme and the arrangement of rhyme (abab, abba) are all expressions of rules closely related to symmetry. And what can be said of music which seems the most spontaneous but is perhaps the most rigorously constructed of all the arts? Rhythm, its essential constituent, is a more or less marked repetition in the beat of notes whose suggestion is, almost automatically, to cause the listener to dance. The fugue of Bach's third sonata for violin and that of the sonata op. 110 by Beethoven are well-known examples of counterpoint which reach the summits of artistic beauty by applying the most rigorous rules of symmetry. First there is the introduction, then the repetition of the theme in its normal form, the elaboration, then the introduction, as a second subject, of the same theme but 'in reverse' (that is to say symmetrical with respect to a horizontal line).

The sense of symmetry is more evident in the figurative arts or in architecture. The ancient temples of Greece and Italy, e.g., the Parthenon on the Acropolis at Athens, and the early Christian churches, e.g., S. Sophia in Constantinople, are shapes with high symmetry. In classical times one could not conceive of something beautiful which was not symmetrical.

Aesthetic rules are much changed today; yet certain rules are still valid, being reinforced by requirements of techniques and construction. The shape of the Anglo-French Concorde, the profile of the Verrazzano bridge in New York or that of the Pirelli skyscraper in Milan are some examples from the many that could be cited.

Symmetry is closely connected to our idea of beauty but what is its importance in science? It is one of the basic rules of the scientific structure; in fact, when Tsung-Dao Lee and Chen Ning Yang in 1957 showed that the principle of parity – strictly related to symmetry – does not hold in a certain area of subatomic physics, a revolution broke out among physicists.

Returning to our own area, however, it is necessary to leave the general approach and to define our terms more accurately.

Symmetry elements and operations

A definition of symmetry immediately requires a qualification: with respect to what is an object considered symmetrical? Is it with respect to a point, a line or a plane? These different references correspond to different symmetry elements which in turn are defined by certain symmetry operations. There are thus different types of symmetry, each defined by a certain operation.

A figure is said to possess a symmetry axis of order n when it is possible to recover exactly the various parts of the figure n times during a complete rotation around a certain axis (or, in an equivalent way, when the various parts of the figure are recovered with a rotation of $2\pi/n$ around a certain axis). A figure has a plane of symmetry when it is possible to recover the parts of the object by means of a reflection in a plane which cuts the figure. In the case of figures which are only two dimensional, a line of reflection takes the place of the plane.

If we examine some capital letters of the alphabet printed with simple characters (Fig. 41), we see that almost all are composed of two parts which can be superimposed by reflection or by rotation. Some only (F, G, L, P, Q, and R, to be precise) are asymmetric.

The following figures illustrate the simplest symmetry operations: rotation and reflection (Figs. 42 and 43 respectively).

With these two elements, a rotation axis and a symmetry plane, and with their combinations, it is possible to describe all the symmetries which can exist for objects of finite dimensions. In the case of one, two or three-dimensional figures considered to have infinite size, however (a visible object can be considered to have effectively infinite size compared to a molecule), a new element and a new operation must be introduced: translation with respect to one, two or three-directions. The case of repetition arising from three-dimensional translation is extremely important because it lies at the base of crystallography, i.e., of the study of matter in the most highly ordered state possible. Simple examples of translation are indicated in Fig. 44.

We have already said that rotation and reflection are the two fundamental symmetry operations for finite bodies. Several axes of rotation or planes of reflection may be present in a particular body; and there can also be other elements derived from these but without the presence of these elements being rigorously necessary. One of the most important of the derived elements is the centre of symmetry or centre of inversion which is also often considered as a fundamental element. (In such a case the symmetry plane would not be fundamental: it is possible, in fact, to construct two equivalent systems of

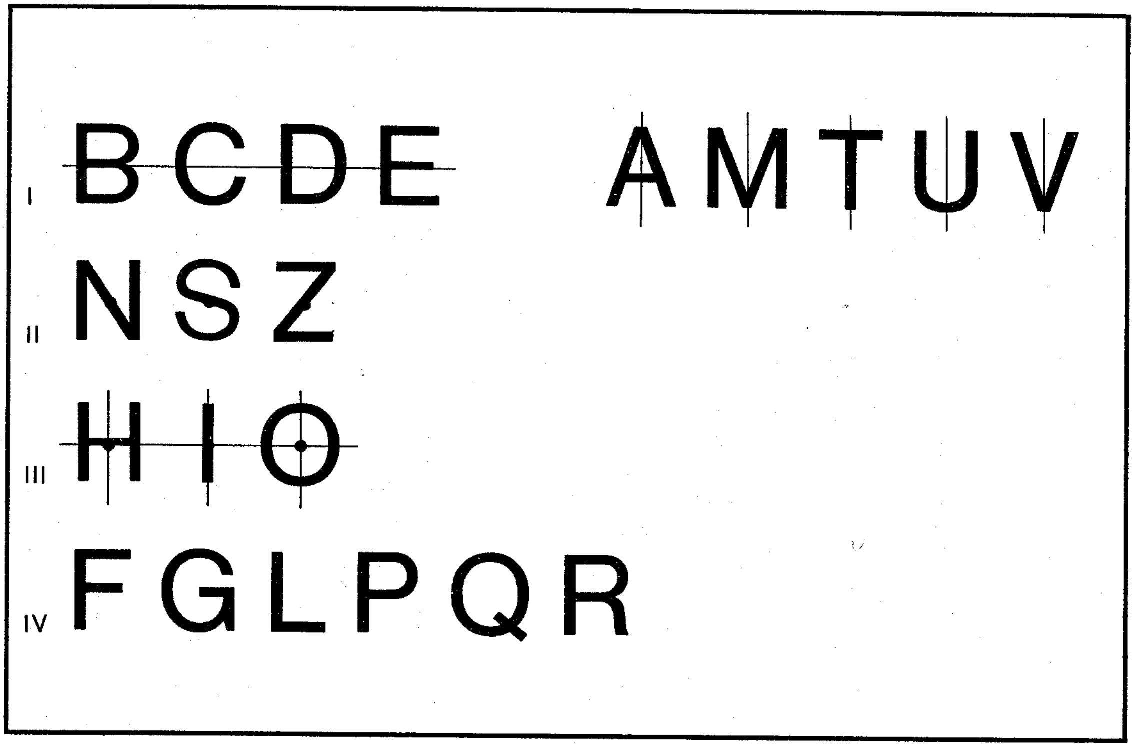
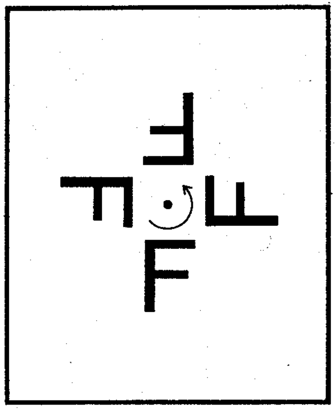


Fig. 41 The capital letters of the alphabet can be divided into four classes based on their type of symmetry. In the first, each letter can be divided by a line into two symmetrical halves; in the second, a rotation of the letter through 180° around a vertical axis passing through the point indicated leaves its shape unaltered; in the third, these two types of symmetry are both present; in the fourth, however, there is no element of symmetry.



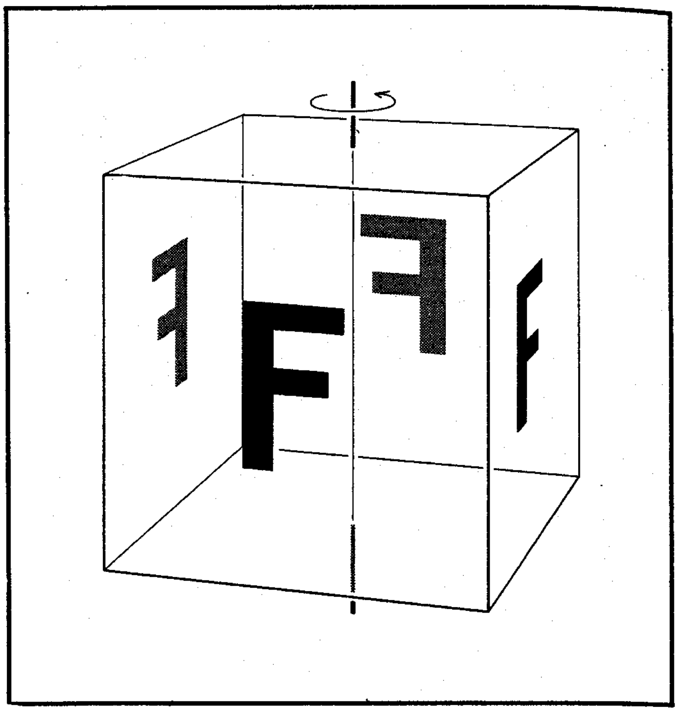
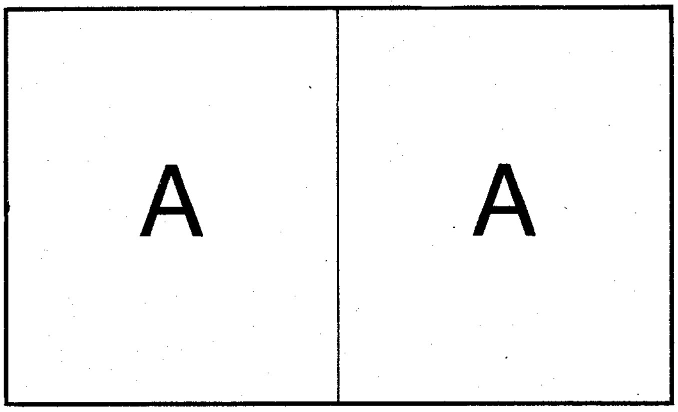


Fig. 42 A square in which four identical letters are drawn in the way indicated represents an example of fourfold rotational symmetry. A fourfold symmetry axis is said to be present. Its projection on a plane is indicated by a point. On the right a cube is shown with four of its faces distinguished by a letter. Here also there is a fourfold rotational axis. In a similar way, twofold or threefold axes lead to a recovering of the figure two or three times, respectively, for each complete rotation.



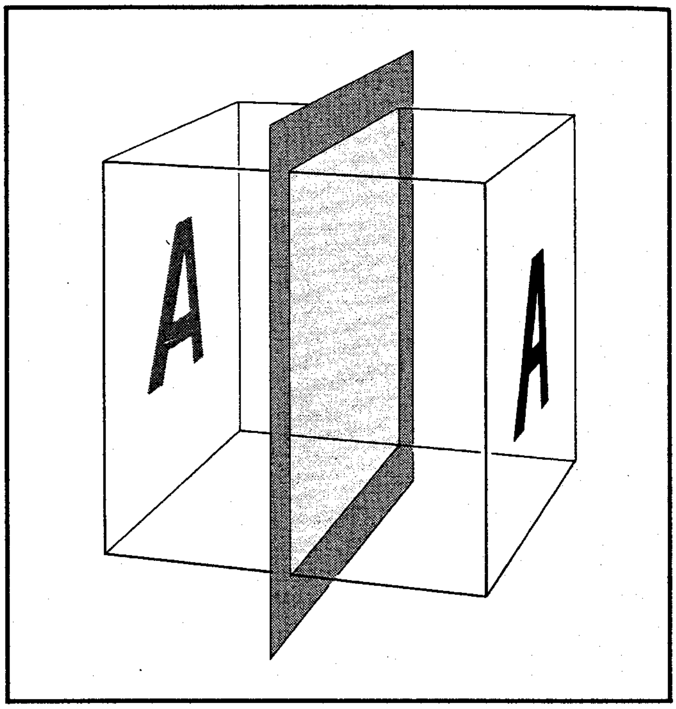


Fig. 43 The rectangle on which the letters A are drawn is divided by a reflection line into two halves which are mirror images of each other: each point on the right of the line is symmetrically connected to one on the left by an operation of reflection. If a three-dimensional figure is considered (see the cube represented on the right), the operation of reflection must be referred to a plane, called a plane of symmetry or a mirror plane. The two letters drawn on the faces are related to each other as object and mirror image.

definitions and of symmetry operations, one based on rotation and reflection and the other on rotation and inversion.)

The centre of symmetry is defined as that point from which, if one moves away in opposite directions, one encounters equivalent elements of the body under examination. A simple example is provided by the dark room and the photographic enlarger; the image is inverted and upside-down with respect to the original. Figure 45 clearly illustrates the differences between a binary rotation, a reflection and an inversion.

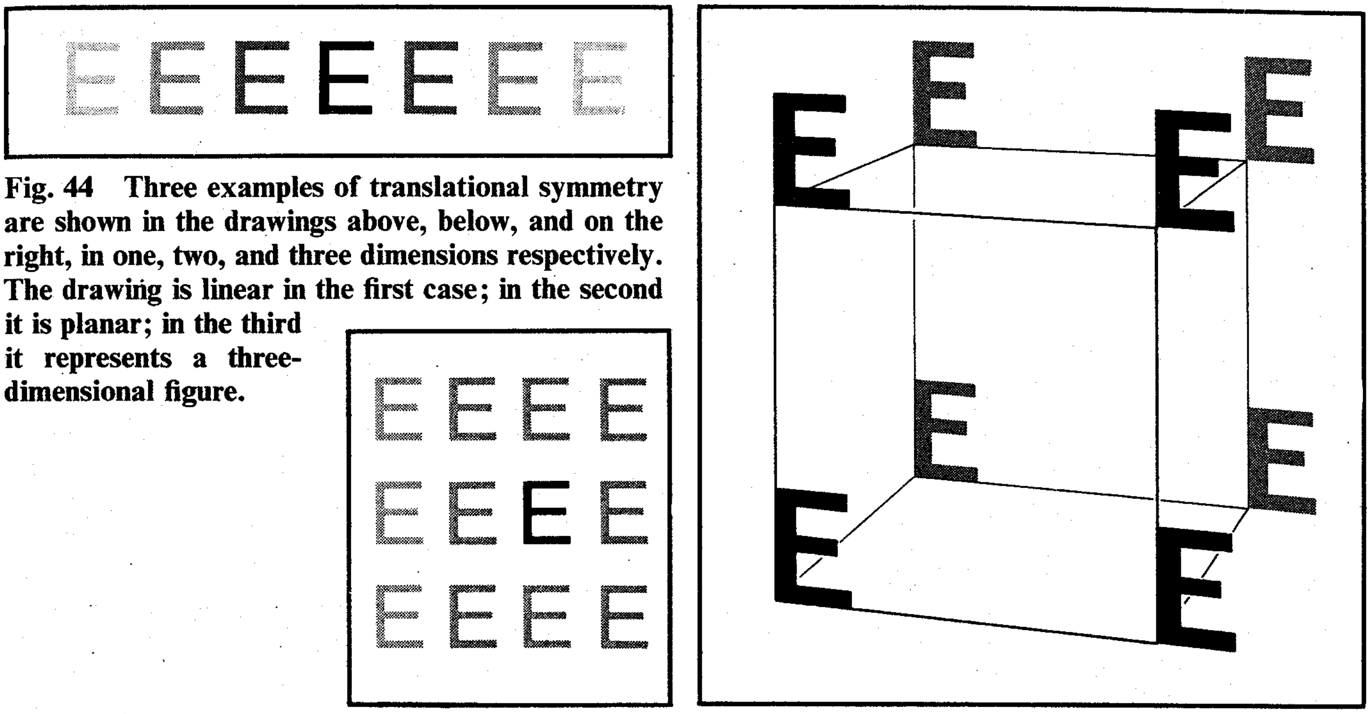


Fig. 44 Three examples of translational symmetry are shown in the drawings above, below, and on the right, in one, two, and three dimensions respectively. The drawing is linear in the first case; in the second it is planar; in the third it represents a three-dimensional figure.

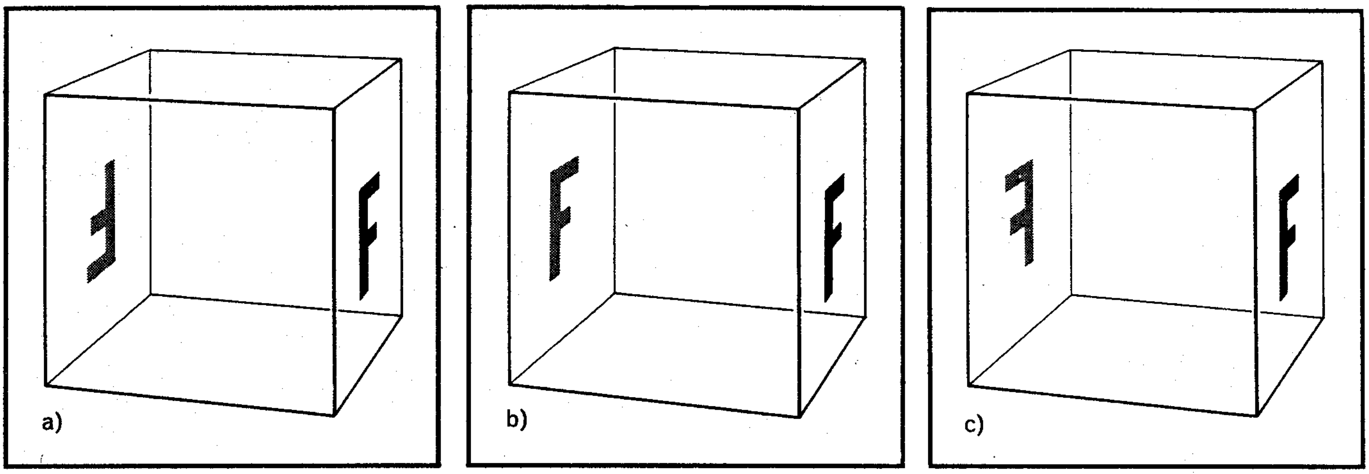


Fig. 45 In (*a*) an example of an object with a centre of symmetry or inversion. Each point of the letter inscribed on one face is connected to one on the other face by a straight line passing through the centre of the cube. This point is the centre of symmetry or inversion. A simple example is furnished by the photographic lens. The difference between the centre of symmetry in (*a*), the plane of symmetry in (*b*) and the binary rotation axis in (*c*) is clearly visible by comparing the three figures.

In the most general way, the combinations of rotation and reflection, very important in stereochemistry, are called improper axes of rotation, rotation-reflection axes or alternating axes. An alternating axis of order n is defined by a rotation through an angle of $2\pi/n$ around the axis, followed by a reflection in a plane perpendicular to the same axis (Fig. 46). The special case of the rotation-reflection axis of order I is equivalent to a plane of symmetry: in fact, the resultant rotation through a complete circle ($2\pi/1$) does not change the position of the object. A twofold alternating axis is equivalent to a centre of symmetry: a rotation of 180° ($2\pi/2$) followed by a reflection corresponds to an inversion. Among the other improper axes, the four-fold axis, defined by a rotation of 90° ($2\pi/4$) followed by a reflection is also important and, in general, so also are the axes of order $4n$.

The symbolism introduced by Schoenflies is much used for treating molecular symmetry. It is particularly useful when these problems are investigated by means of mathematical group theory, the most advanced area of that formalization of chemical knowledge which we indicated earlier. We feel it is useful to explain the fundamentals of the symbolism in Appendix III (p. 245). The symbolism will be used in this book but only in moderation and will be accompanied each time with a more descriptive treatment.

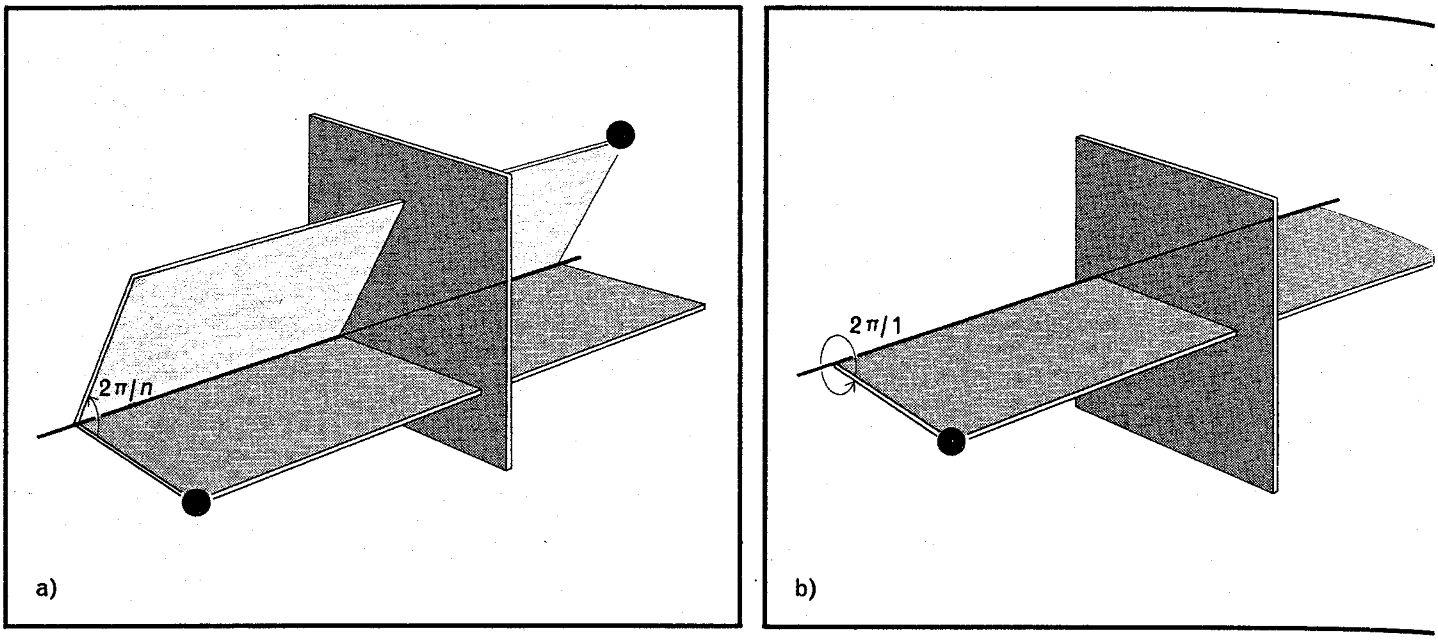
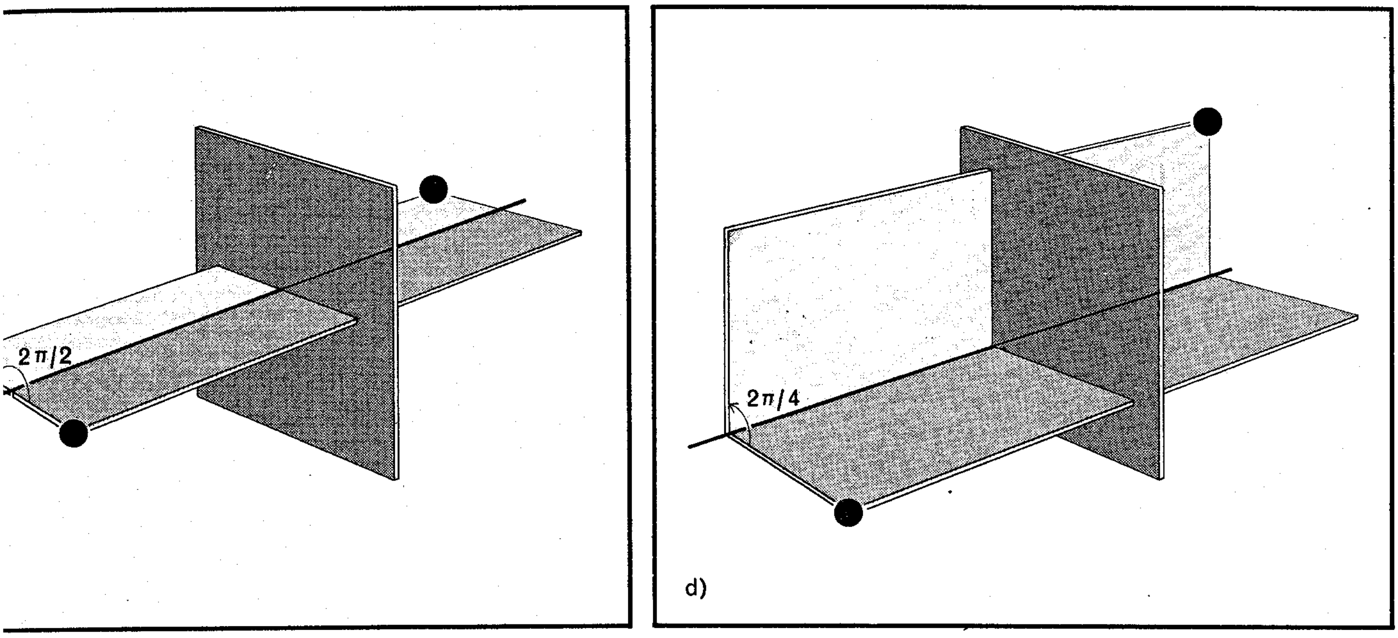


Fig. 46 **The rotation-reflection axis, also called an alternating axis, is defined by the combination of two symmetry operations. Firstly, a rotation through a given angle ($2\pi/n$ where n is the order of the axis) is carried out, followed by a reflection in the plane perpendicular to the axis, as illustrated in (*a*). In (*b*), (*c*) and (*d*),**

Molecular symmetry and optical activity

Until now we have spoken about bodies and figures in a quite general manner but we were obviously thinking about molecular structures as the particular objects to which to apply our thoughts. Actually such considerations are applicable only to rigid bodies and molecules cannot be considered as such, if for no other reason than because of the vibrational motion of the atoms around their equilibrium positions. But even neglecting this factor, we know that many types of molecule have freedom of rotation around certain bonds between the atoms (for example, around the single C—C bond) and can thus undergo radical alteration of their shapes. Some of these forms are more stable than others; in the liquid and gaseous state there is often a mixture of different, rapidly interconverting, forms as described in the preceding chapter. As a first stage in the analysis of symmetry it is necessary to consider the molecule as a rigid body; if different conformations are possible, they must be examined separately. In certain cases, however, the problem can be overcome by a simplified approach, as we shall show later.



alternating axes or order I ($n = 1$), II ($n = 2$) and IV ($n = 4$) are shown. An alternating axis of order I is equivalent to a plane of symmetry (one complete revolution does not alter the position of an object) and that of order II to a centre of symmetry (rotation through 180° followed by reflection corresponds to an inversion).

We have already defined the necessary condition for a compound to be optically active. The molecules of which it is composed must not be superimposable upon their mirror images.

There are two ways of verifying this lack of reflective symmetry. We may either construct a pair of mirror-image models and verify whether or not they are identical or, more elegantly, we may show the existence of certain elements of symmetry in the molecule. In fact, it can be demonstrated that reflective dissymmetry or enantiomorphism is related to the absence of alternating axes of any order.

The need for such a general statement (absence of alternating axes of any order) was first felt no more than fifteen years ago. Until that time the generally accepted necessary condition for molecular dissymmetry was the absence of planes or a centre of symmetry. We showed above that these axes coincide respectively with alternating axes of order I or II; it is easily seen that many alternating axes of higher order – more precisely those of any order except 4*n* – may also be reduced to such elements. But the alternating axis of order IV and those (rarer) of 4*n* cannot be reduced to a plane or to a centre of symmetry. In 1956 McCasland prepared a spiran compound – which consists of two rings attached to a single atom – without planes or a centre of symmetry but which could still not be resolved into optical antipodes because of the presence of an alternating axis of order IV (Fig. 49, group S_4).

What we have said certainly does not mean that the condition for optical activity is the absence of every symmetry element but rather it is the absence of those which cause the object and its mirror image to be identical. For this reason we frequently use the terms chiral or dissymmetric, rather than asymmetric, as this latter is a restricted definition. An object is asymmetric when it contains no symmetry elements at all, not even rotation axes which do not influence the prediction of optical activity. An object is chiral or dissymmetric when it does not contain alternating axes of any order – but it may still have simple rotation axes.

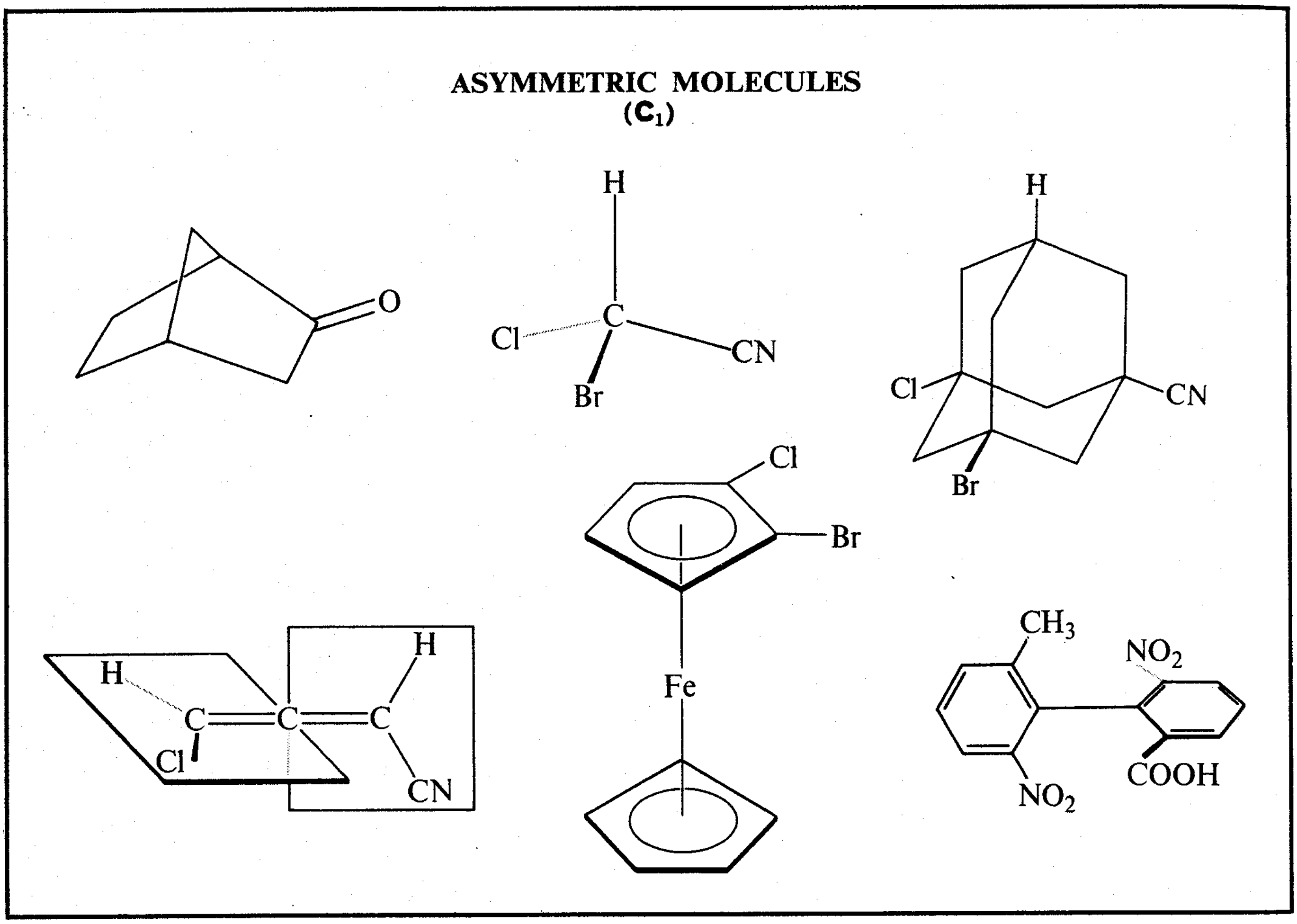


Fig. 47 Asymmetric molecules do not contain any element of symmetry. According to the Schoenflies system (see Appendix III, p. 245) these belong to the group C_1. A series of rigid asymmetric structures is shown: *nor*-camphor, chlorobromoacetonitrile, chlorobromocyanoadamantane, 1-cyano,3-chloroallene, 1-chloro,2-bromoferrocene and 2,2′-dinitro-6-methyl-6′ carboxybiphenyl.

In the Schoenflies notation (see Appendix III, p. 245) asymmetric molecules belong to the $\mathbf{C}_1$ group and those which are dissymmetric belong to the groups $\mathbf{C}_n$ and $\mathbf{D}_n$. Other chiral groups actually exist, but no example of molecules belonging to them is known at present. Some examples of particularly significant molecular structures are shown in Figs. 47, 48 and 49.

How to treat non-rigid molecules

If the reader has studied chemistry to a certain level he may be amazed by the examples of optically active compounds given in these pages. With all the available natural products (amino acids, sugars, terpenes and steroids) was it really necessary to choose *nor*-camphor, dichloroallene, or helicene in order to illustrate the phenomenon?

This objection is certainly valid. In many organic chemistry text books the treatment is based on lactic acid (a product of carbo-

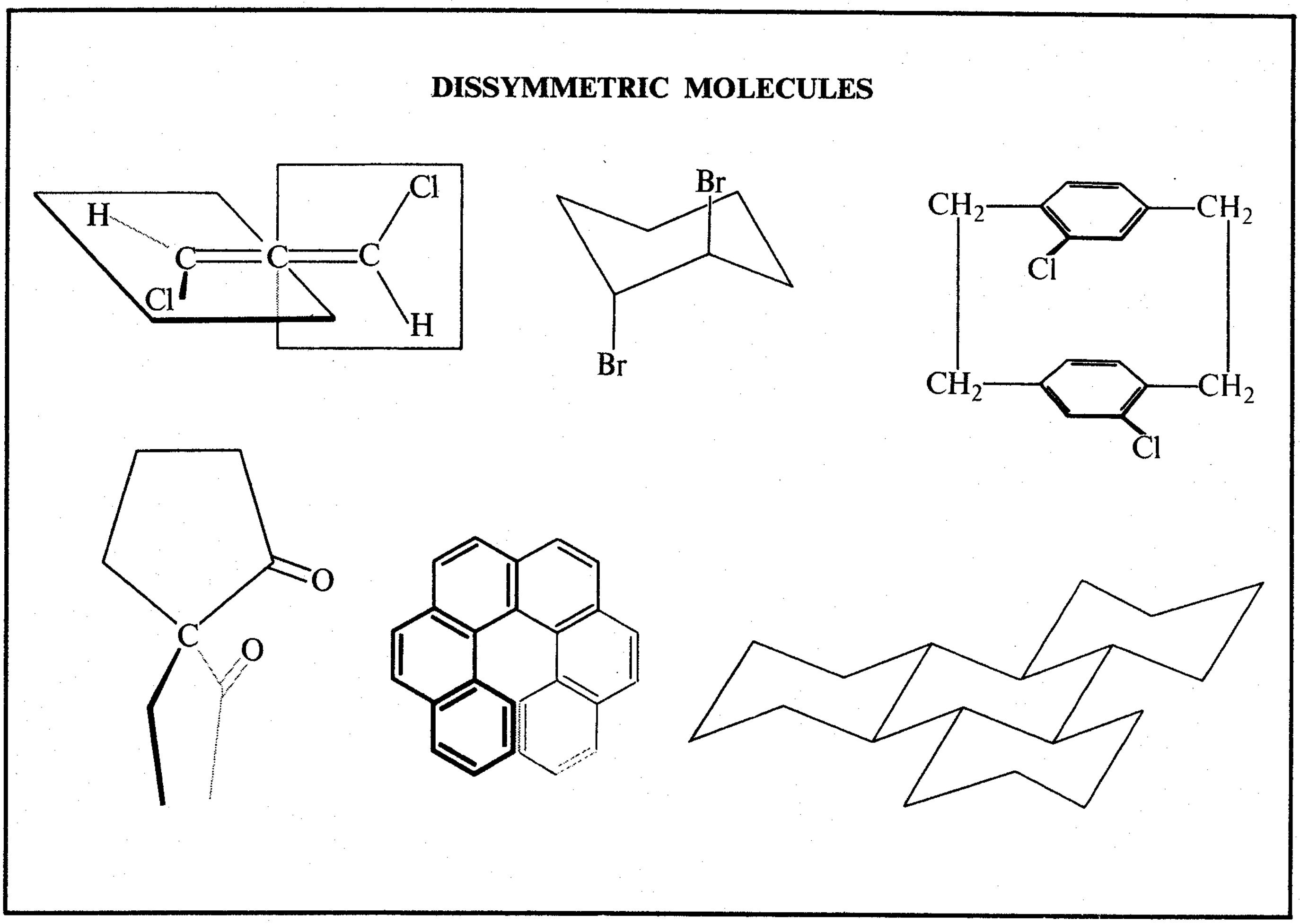
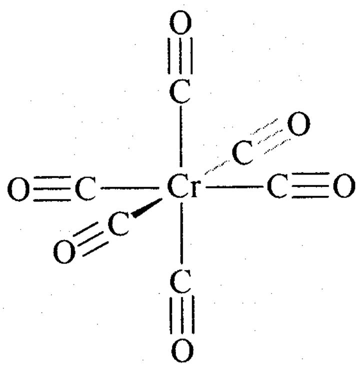
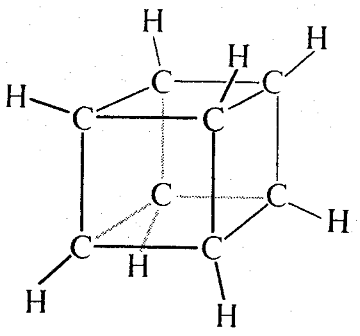
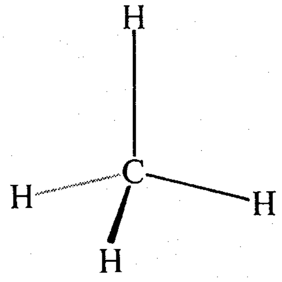


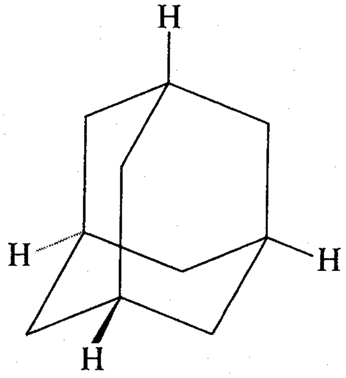
Fig. 48 Dissymmetric molecules do not have alternating symmetry axes but only simple rotation axes. Some compounds of the group $\mathbf{C}_2$ are shown: dichloroallene, 1,2-*trans*-dibromocyclohexane, a dichloroparacyclophane, a spiran ketone and hexahelicene. The last compound belongs to the group $\mathbf{D}_3$ and is one of the ten isomers of perhydrotriphenylene, the organic molecule with the highest symmetry so far resolved into optical antipodes.

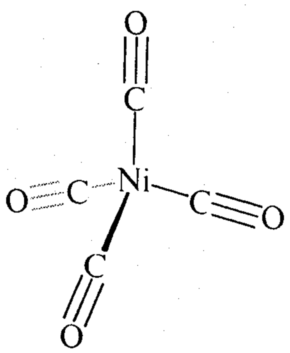




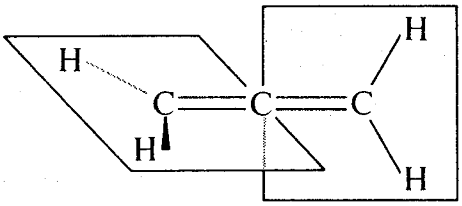
O_h ________________________________

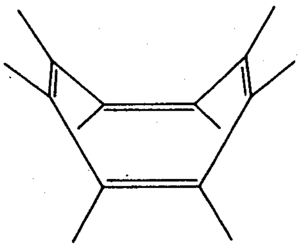


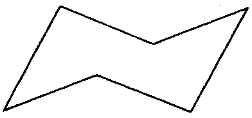




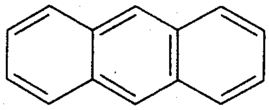
T_d ________________________________

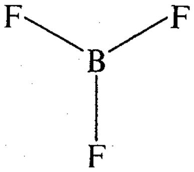


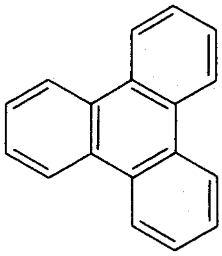


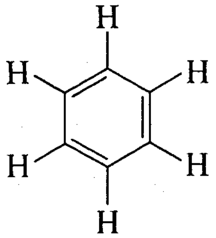


D_{2d} ________________________________ **D_{3d}** ________________









D_{2h} ____________ **D_{3h}** ________________________ **D_{6h}** ____________

$H—C\equiv C—H$ $O=C=O$

$N\equiv N$

$D_{\infty h}$ ________________________

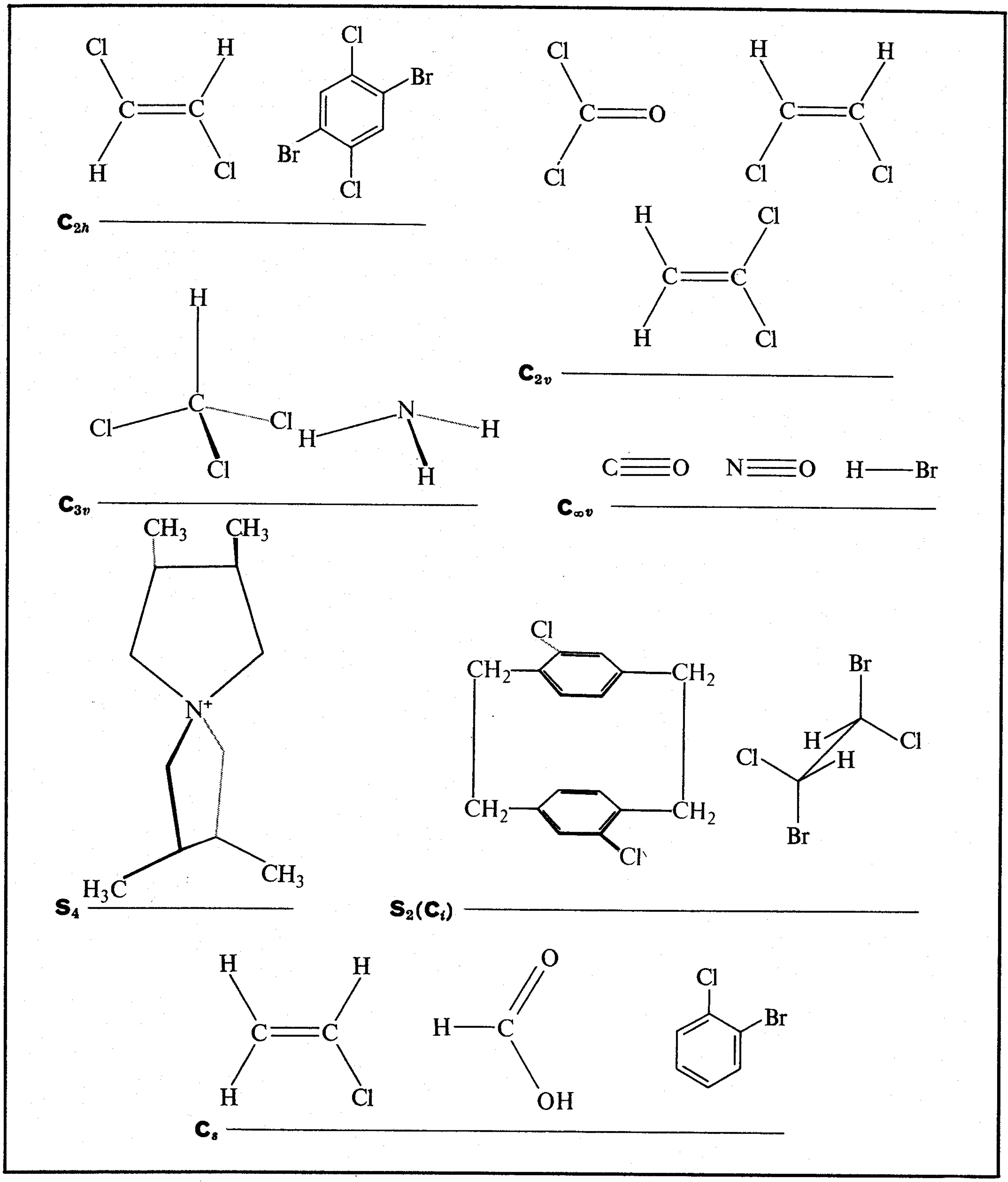


Fig. 49 Examples of non-dissymmetric molecules. Chromium hexacarbonyl and cubane belong to the octahedral group (O_h); methane, adamantane and nickel tetracarbonyl to the tetrahedral group (T_d); allene and cyclo-octatetraene to D_{2d}; cyclohexane to D_{3d}; anthracene to D_{2h}; boron trifluoride and triphenylene to D_{3h}; benzene to D_{6h}; acetylene, carbon dioxide and nitrogen to $D_{\infty h}$ (cylindrical symmetry). The following are examples of other groups: C_{2h}, *trans*-dichloroethylene and 1,4-dichloro,2,5-dibromobenzene; C_{2v}, phosgene, *cis*-dichloroethylene, vinylidene chloride; C_{3v}, chloroform and ammonia; $C_{\infty v}$ (conical symmetry), carbon monoxide, nitric oxide and hydrogen bromide. The tetramethylspiropyrollidinium ion belongs to the S_4 group; in the C_i group there is a dichloroparacyclophane and a conformation of 1,2-dichloro,1,2-dibromoethane; finally, in the C_s group are vinyl chloride, formic acid and *ortho*-chlorobromobenzene.

hydrate metabolism), tartaric acid and *iso*-amylalcohol (all by-products of alcoholic fermentation) and so on. But the reason for our preference is strictly related to the criteria of symmetry. We have repeatedly said that our account refers to rigid structures, like those shown earlier, and not to flexible or mobile structures, like some of those just cited. But how should we then face the problem of flexible or mobile structures given that the majority of dissymmetric molecules are not rigid?

In the chapter on conformational analysis we saw that a simple molecule like ethane (CH_3-CH_3) exists in a stable conformation with the hydrogen atoms staggered across the C—C bond and in an infinite number of high energy (less stable) conformations. One of these forms, that with the hydrogen atoms covering each other across the C—C bond (eclipsed), is particularly obvious. If we examine their symmetry properties (see Fig. 50), we can easily see that the staggered and the eclipsed forms are not dissymmetric (groups $\mathbf{D}_{3d}$ and $\mathbf{D}_{3h}$ respectively), while the intermediate forms are chiral (group $\mathbf{D}_3$). Conformational analysis tells us that the non-dissymmetric, staggered, forms are stable but, given rapid rotation around the C—C bond, we can assume to a first approximation that the threefold symmetry of the methyl group-CH_3 changes to conical symmetry. A general example of this increase in symmetry is given by the bicycle wheel. The arrangement of the spokes is quite visible when the wheel is stationary (group $\mathbf{S}_n$) but on rapid rotation the design of the spokes disappears and the wheel looks like a disc (group $\mathbf{D}_{\infty h}$). What we have said can be applied to other groups of atoms rapidly rotating around bonds. For example, lactic acid is still asymmetric even if the conformations of the methyl, the hydroxyl, and the carboxyl groups are neglected (Fig. 51). But, in spite of this simplification, new factors arise when somewhat more complex molecules are considered.

Returning again to conformational analysis, let us consider the butane molecule (Fig. 52). We know that it exists in three different stable conformations, one (*trans*) planosymmetric ($\mathbf{C}_{2h}$) and two dissymmetric *gauche* ($\mathbf{C}_2$), these latter being mirror images of each other. A single molecule of butane in the *gauche* conformation is optically active but it can convert into its optical antipode and into the *trans* form. The time-average for the optical activity of a single molecule is thus zero. The simultaneous presence of many molecules distributed in equal proportion between the two enantiomorphic conformations thus ensures the optical inactivity of butane.

We are now in a position to return to the starting point: to Pasteur and his tartaric acids.

The stable molecular conformations of (+)-tartaric and (−)-tartaric acid are shown in Fig. 53. They are both dissymmetric

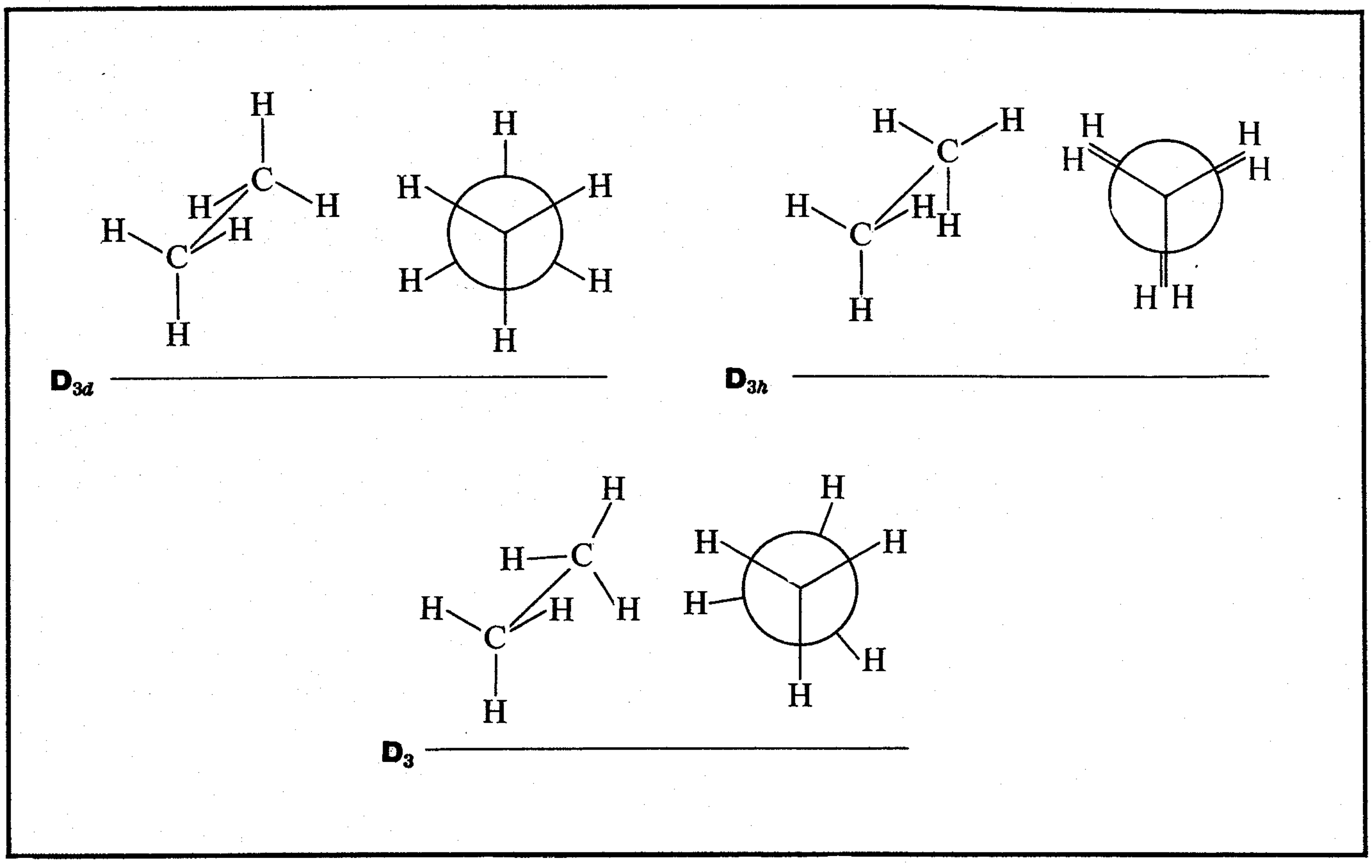


Fig. 50 **The stable conformation of ethane has D_{3d} symmetry; in particular, it has three planes of symmetry which each contain the carbon atoms and two hydrogen atoms. The higher energy eclipsed conformation belongs to the group D_{3h} and has an additional plane of symmetry which cuts the C-C bond. The intermediate unstable forms have D_3 symmetry, i.e., they have rotation axes but not mirror planes; these are optically active. However, given the ease of internal rotation around the C-C bond it can be considered that the ethane molecule has the symmetry of its stable form (D_{3d}) or even a cylindrical symmetry ($D_{\infty h}$), as though it consisted of two spheres connected by a rod.**

(group C_2 if secondary deformations are ignored) and so also are the transition states from one stable conformation to the other. Each conformation of the (+) acid is exactly enantiomorphous with a conformation of the (−) acid but there is no compensation between the different forms in either the (+) or the (−) acid. We can conclude that (+)-tartaric acid *may be* optically active. We say *may be* – and the conclusion will seem rather weak after so many words – because the treatment of symmetry made at this level cannot tell us anything about the magnitude of the optical activity. Our argument, in fact, contains a necessary but not a sufficient condition for optical activity. Beyond the factors we are studying there are others of a physical – as opposed to purely geometrical – nature which determine the value of the rotation. Cases are well known in which random compensation of different factors may render a compound inactive, even if symmetry consideration indicate the presence of activity.

Let us now look at the structure of *meso*-tartaric acid. Its most

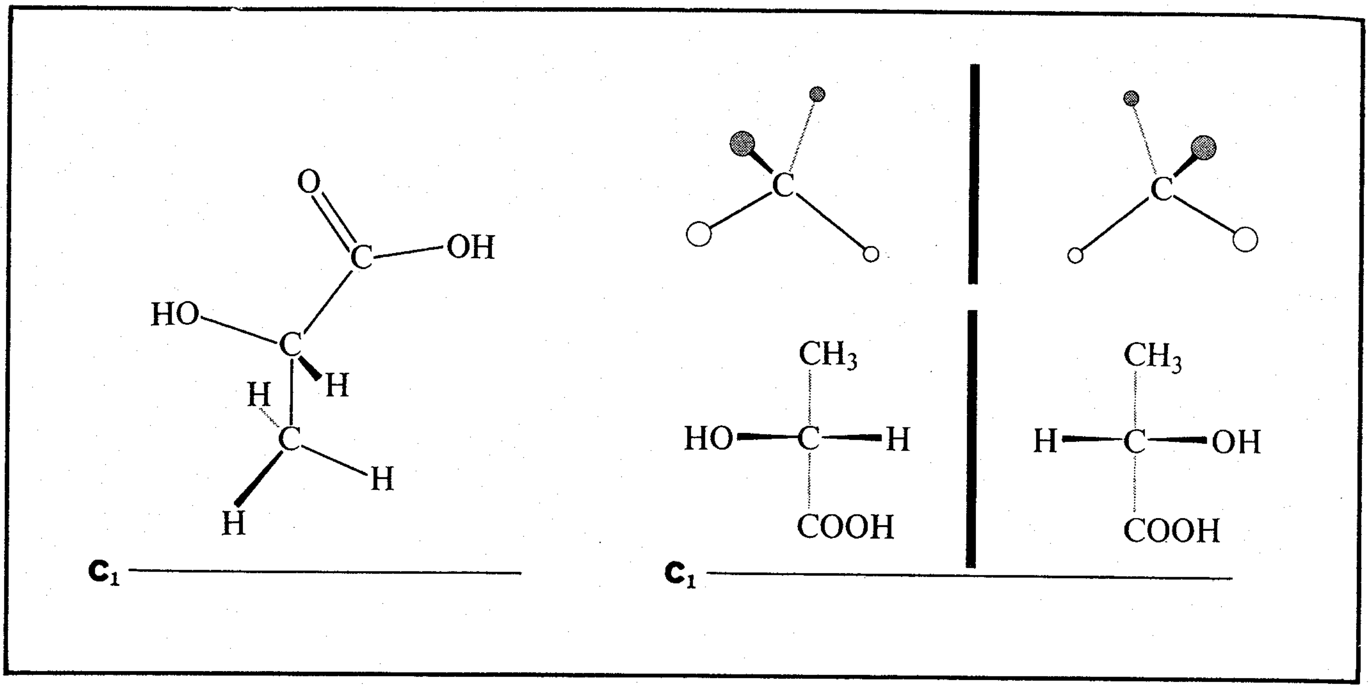


Fig. 51 One of the conformations of lactic acid in which there is no element of symmetry (group C_1). Even if the various groups were allowed to rotate about the bonds which join them to the central atom, the structure would always be asymmetric. Four different spheres placed at the corners of a tetrahedron constitutes, in fact, an asymmetric system. At the bottom right, the formulae of the two optical antipodes of lactic acid are shown. The central atom bonded to four different substituents (-H, -OH, $-CH_3$ and -COOH) is called an asymmetric carbon atom.

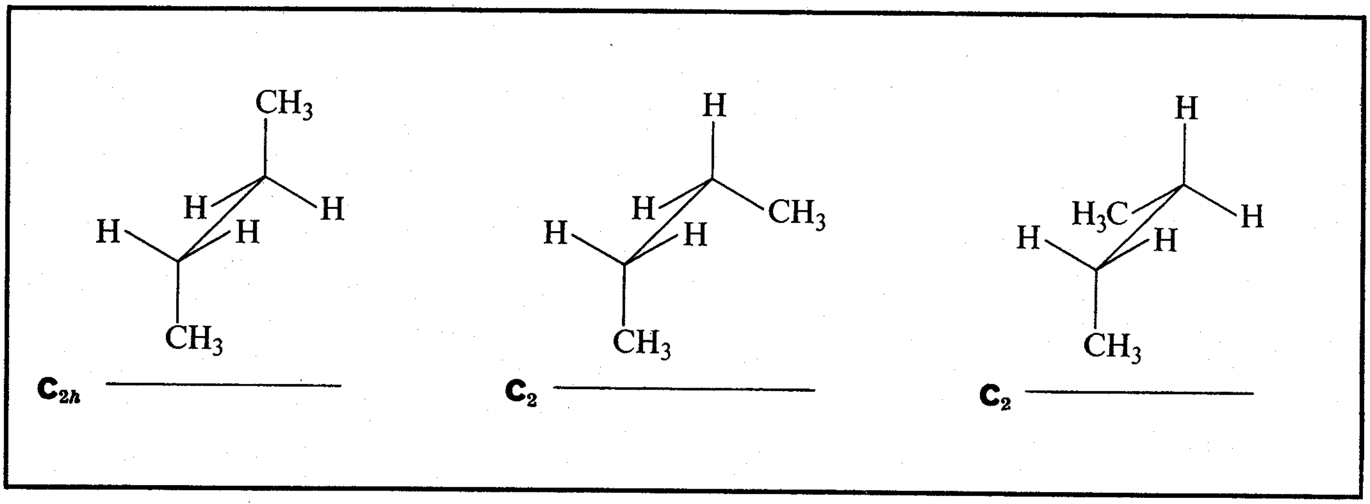


Fig. 52 Of the three stable conformations of butane (C_4H_{10}) the *trans*, with the lowest energy content, is planosymmetric while the two *gauche* conformations are dissymmetric (group C_2). The latter form a pair of optical antipodes: they have equal energy and are thus present in equal quantity. The contribution of the optical activity of the one form is exactly balanced by that of the other and, moreover, these two forms interconvert very rapidly both between themselves and the planosymmetric form. Butane is thus optically inactive.

stable conformations and one of the intermediate states are shown in Fig. 53. In contrast to the preceding case, and in a way very similar to butane, we find a non-dissymmetric (C_i) conformation and two asymmetric conformations (C_1); these latter are enantiomorphs. The transition state is also non-dissymmetric or non-chiral. (Although these terms are a little clumsy, they are the only precise ones. They

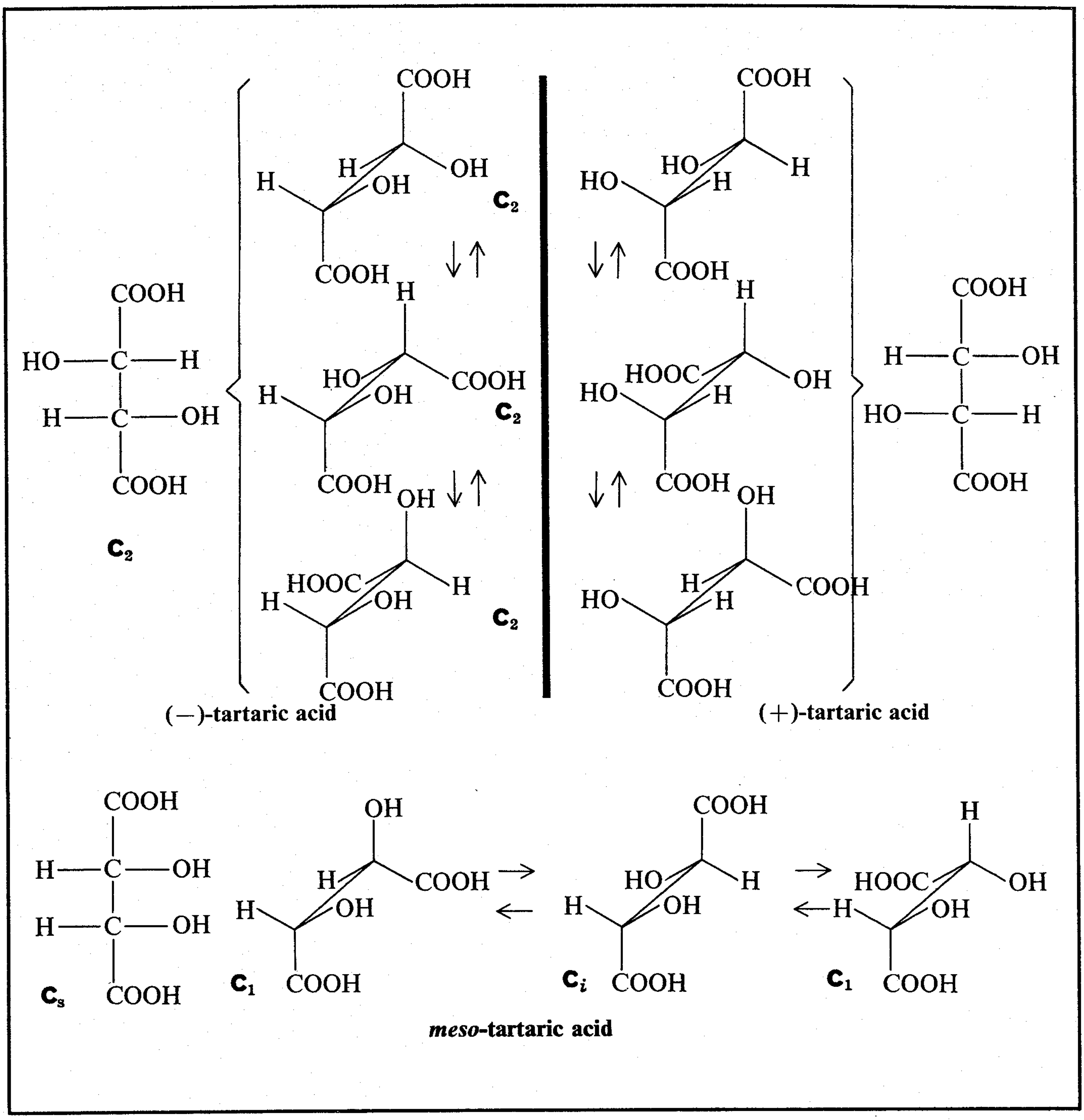


Fig. 53 Fischer projections and perspective formulae of the tartaric acids. At the upper left, (−)-tartaric acid is shown. The stable conformations are all dissymmetric (C_2) and easily convert from one to another by internal rotation around the central C-C bond; but they cannot change into the mirror-image forms. These mirror images correspond to another compound, (+)-tartaric acid, which cannot transform into the first. Below: *meso*-tartaric acid (inactive) can exist in three interconvertible conformations. One of these is centrosymmetric; the other two are asymmetric and constitute a pair of optical antipodes.

cannot be replaced by 'symmetric' because all molecules, except for group C_1, contain some elements of symmetry. Dissymmetric and non-dissymmetric, or chiral and non-chiral, refer only to the absence or presence of alternating axes.) The relatively small value for the potential barrier to internal rotation around the central bond assures us that there is a rapid exchange from the enantiomorphic forms to the symmetrical form and that there is a rapid exchange between the enantiomorphic forms. *Meso*-tartaric acid is therefore inactive because it is formed from a mixture of rapidly interconverting symmetric and dissymmetric forms. If, however, *meso*-tartaric acid were to be examined at a very low temperature, a temperature at which the molecules did not have sufficient energy to overcome the barrier to internal rotation, it would be possible to isolate three *meso*-tartaric acids: one inactive (corresponding to the C_i conformation), one dextro and one laevo. An analogous phenomenon actually occurs at room temperature for certain derivatives of biphenyl. But we shall speak about this later.

The presence of a stable, achiral form is not really necessary to ensure inactivity of a compound. *Cis*-1,2-dichlorocyclohexane exists in two enantiomorphic conformations which can interconvert at room temperature without passing through any stable symmetrical form. In this case, only the transition state between one form and its optical antipode displays mirror symmetry (Fig. 54). We can state a general rule: the sufficient condition for optical inactivity of a compound with free internal rotation is the presence of non-dissymmetric conformations, no matter whether they are stable or not, or the presence of dissymmetric conformations in equilibrium with their optically antipodal forms.

According to the classical treatment, *meso*-tartaric acid and *cis*-1, 2-dichlorocyclohexane have two asymmetric carbon atoms, the one with a (+) and the other with a (−) sign; their effect is to nullify each other and the compound is thus inactive. This interpretation is less sophisticated than the preceding one but, when applied to the prediction of optical activity, leads to the same conclusions.

When the chain of atoms becomes longer a detailed examination, of the type made in the case of the tartaric acids, becomes ever more complex. The number of possible conformations increases rapidly (by a factor of 3, or a little less, for each additional carbon atom) and for a system of no more than 6 atoms, as in the case of sugars, a study of all the forms requires the use of a computer.

It is therefore convenient to return to a simpler system, the asymmetric carbon atom, having made the essential nature of the phenomenon quite clear.

The usual definition of an asymmetric carbon atom is that it is an atom bonded to four different substituents. But there are some cases in which this definition does not hold. Even the definition used by Mislow which can be found in some old tests, in which an atom is defined as asymmetric when an exchange of the positions of two substituents leads to a different stereoisomer, requires qualification. It does not apply if the atom lies on an element of reflective symmetry

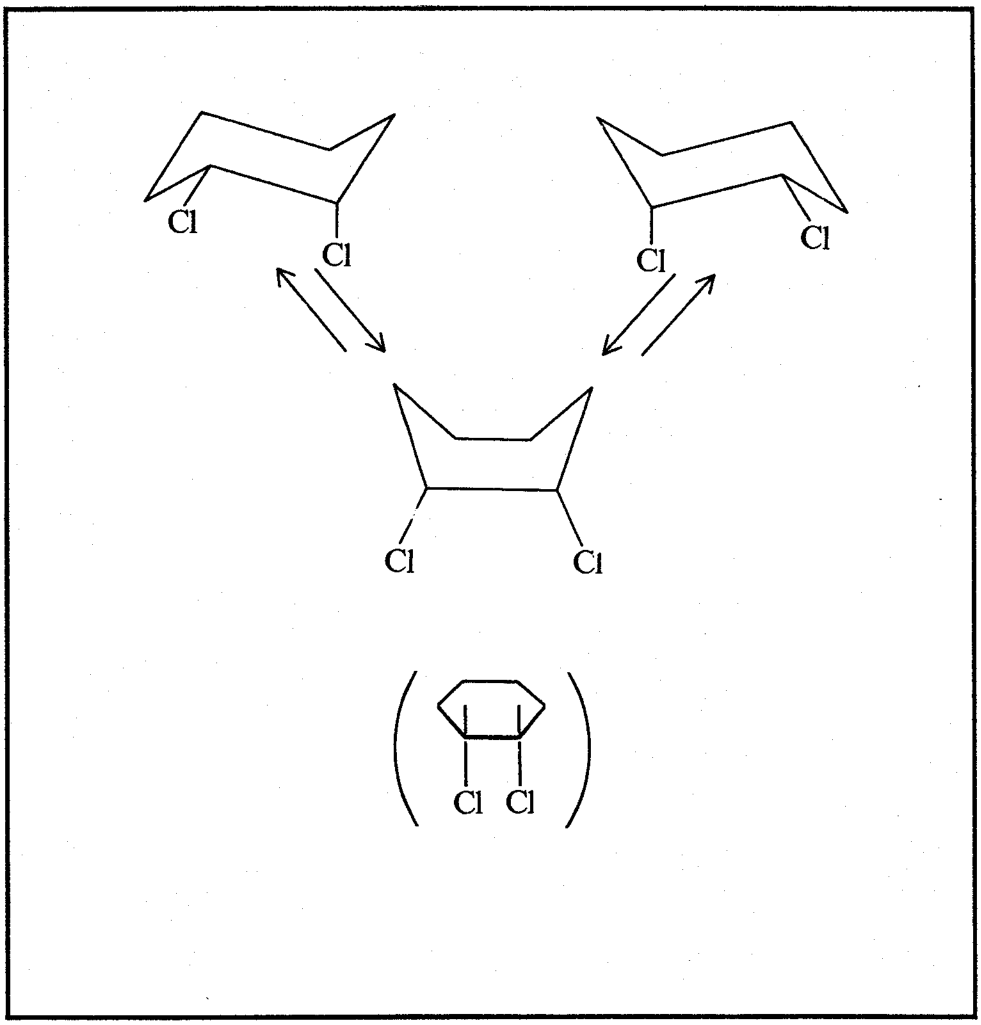


Fig. 54 *Cis*-1,2-dichlorocyclohexane exists in two stable, chiral conformations which can interconvert. In this case there is no non-dissymmetric, stable conformation. Yet it is possible to visualize a non-dissymmetric transition state (unstable).

such as a plane of symmetry. However it is defined, the asymmetric carbon atom is neither a necessary nor a sufficient condition for molecular dissymmetry. Still less is it the cause of optical activity. What one can say with certainty is that the presence of one or more asymmetric atoms (providing they do not compensate each other) leads to a non-zero result for the average dissymmetry of the molecule. In other words, the presence of an asymmetric carbon atom stabilizies certain dissymmetric conformations; moreover, when an asymmetric atom is present, in contrast to the case of butane, some compounds do not have conformations which are exactly enantiomorphs of each other (Fig. 55).

Having appreciated the implications of this discussion, one can turn to the Fischer projections which have been successfully in use for more than half a century. These projections, already illustrated on page 22, omit conformational factors and serve only for a configurational study of molecules. In conformational terms the Fischer projections correspond to eclipsed forms, generally unstable, and can be considered as hypothetical transition states. From what we have said previously, if the Fischer projection is symmetrical, there are no configurational isomers in the absence of high barriers to internal rotation. As an example, let us consider the four isomers of trihydroxyglutaric acid (Fig. 56). The first are a pair of D and L optical antipodes: only two asymmetric atoms exist in these, those in positions 1 and 3. Exchanging the substituents on atom 2 does not lead to a new compound; thus atom 2 is not asymmetric; it is bonded to two equal radicals with the same chirality. The other two forms are *meso*-, i.e., internally compensated, forms. An analogous approach to that of *meso*-tartaric acid could be used for these to show that they consist of many types of conformations, both dissymmetric enantiomorphs and non-dissymmetric forms in rapid exchange. On the other hand, using the Fischer projection, one can recognize the existence of a symmetry plane and the two parts of the molecule are mirror images; if atom 1 is dextro, atom 3 will be laevo. Atom 2 is thus bonded to two enantiomorphic substituents (in addition to hydrogen and the hydroxyl). It is called a *pseudo*-asymmetric atom, having only some of the properties of a true asymmetric atom. For example, contrary to a truly asymmetric atom, it lies in a plane of symmetry. *Pseudo*-asymmetric atoms permit the existence of the phenomena of diastereoisomerism but not of enantiomorphism.

A further increase in chain length does not introduce any new factors until the molecule becomes extremely long. But long molecules are extremely important. These macromolecules or polymers are constituents of biological organisms (proteins, starch and cellulose), plastic material, rubbers and natural and synthetic fibres. Thus a special discussion must be devoted to them.

Optical isomerism without asymmetric atoms

The history of organic chemistry contains many accounts of major theoretical and practical obstacles. One of these obstacles was the explanation of the isomerism of biphenyl derivatives. Today, however, it is clear; an examination of their conformations and symmetry allows us to come to an immediate conclusion. Since a derivative of biphenyl can exist in optical antipodes, although no asymmetric carbon atom is present, dissymmetric enantiomorphs must exist which are separated by potential barriers so high that the molecule cannot overcome them in the experimental conditions under which observations are made. But this was not so clear forty years ago when the first solution to the problem was given. At that time the term conformation did not exist and the symbolism of

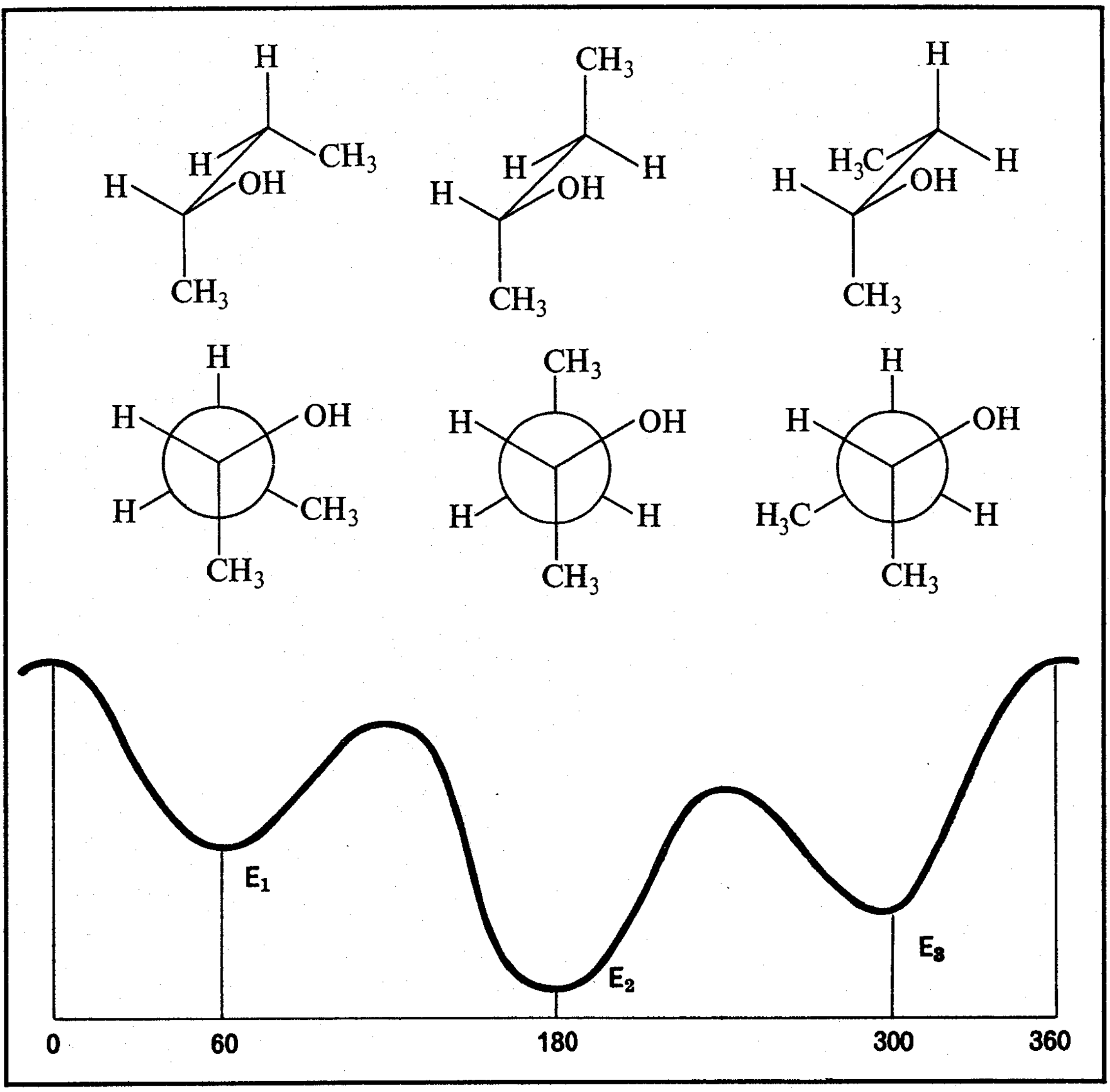


Fig. 55 The three stable conformations of *sec*-butyl alcohol are all dissymmetric: no two of them form a pair of optical antipodes. This depends on the presence of an asymmetric carbon atom. The energy of each of the three conformations is different and the energy diagram is not symmetrical.

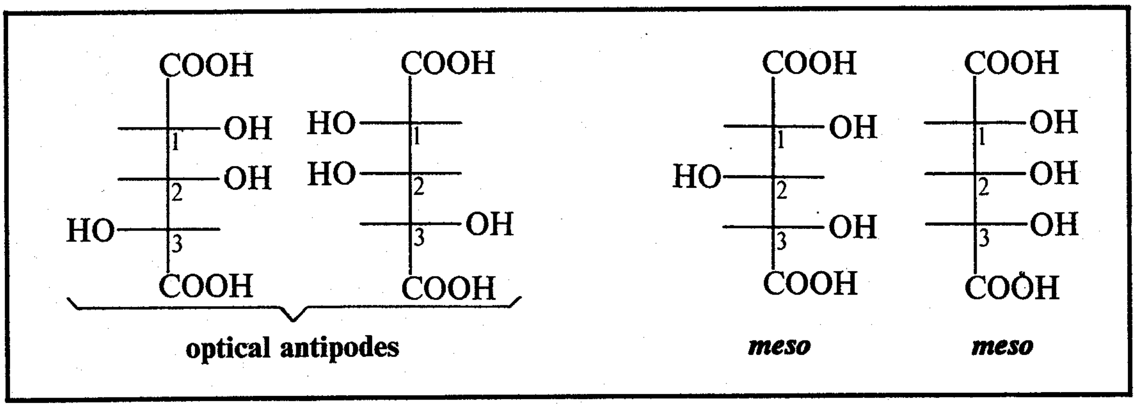


Fig. 56 The Fischer projection represents an unstable hypothetical conformation of the molecule. If it contains elements of reflective symmetry, the molecules are not optically active; they will have dissymmetrical conformations, which form pairs of optical antipodes, and one or more non-dissymmetrical conformations. If the barriers to internal rotation are low, the forms can interconvert and the compound is inactive (*meso*). If, on the other hand, the Fischer projection is dissymmetric, the compound is optically active. Therefore, there are two configurational optical antipodes.

symmetry was unfamiliar to chemists, although familiar to crystallographers.

The need to explain the experimental data concerning the isomerism of biphenyls came into conflict with the logical scheme of aromatic chemistry which had been built up at that time. It had been agreed that molecules had a third dimension but why should the derivatives of biphenyl display isomerism if aromatic compounds were especially characterized by their planar structure?

The exact three-dimensional shape of biphenyl is still not absolutely certain. But one thing is quite clear; in biphenyl and its compounds the two benzene rings are not co-planar but are rotated with respect to each other to an appreciable extent. If one accepts a degree of simplification, one can say that the two rings are aligned along the axis of the molecule but are rotated through a right angle with respect to each other. The presence of suitable substituents raises the barrier to rotation and prevents the molecule from passing into the enantiomeric form and thus destroying the mirror symmetry (Fig. 57). But, where are the asymmetric atoms? They do not exist. Where then is the point of asymmetry? Rigorously, this is an indefinable entity; we can see a centre of symmetry but not a centre of asymmetry. In the case of biphenyls the asymmetry must be considered as extending over the entire molecule. The possibility of isomerism cannot be confined to a particular atom but resides in the general form of the molecule. So we speak of *atropoisomerism,* an asymmetry without a precise location.

Although we have discussed the biphenyls the phenomenon is not limited to this class of compounds. A similar argument can be used in the case of the allenes (Figs. 47 and 48) even though the barriers here are extremely high and are independent of the substituents.

A class very similar to the allenes consists of the spirans – bicyclic

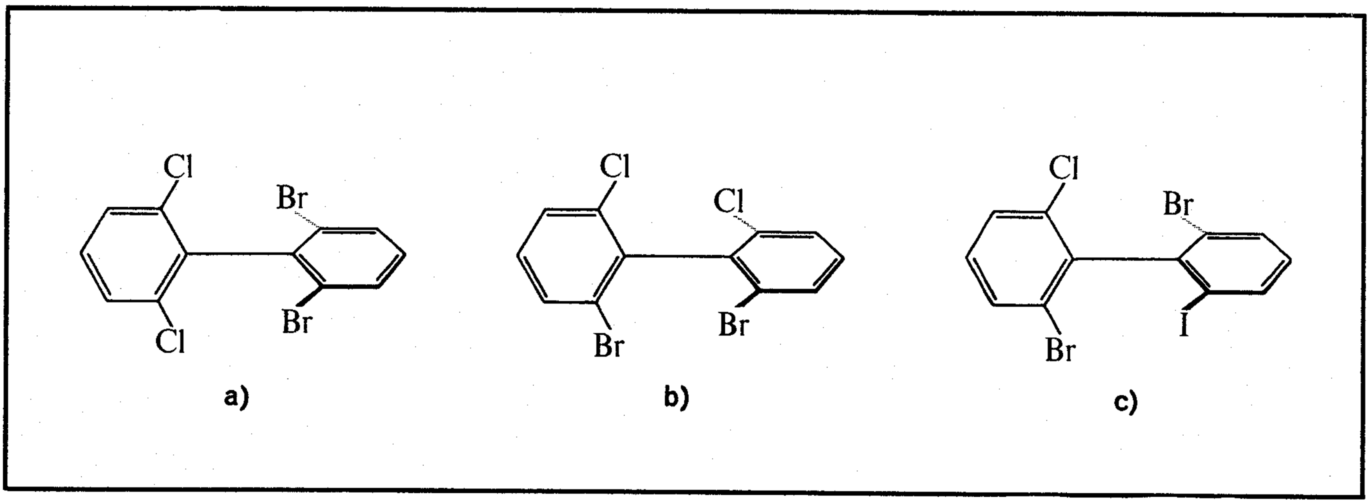


Fig. 57 Three examples of biphenyl derivatives with different symmetry. In (*a*), non-dissymmetric (*b*), dissymmetric; and (*c*) asymmetric. Other examples of atropoisomerism are given in Figs. 47 and 48.

compounds whose rings are attached to only one atom (in a certain sense the double bond of the allenes can be considered as a ring of two atoms) – and the same type of phenomenon also exists for these. Helicene (Fig. 48), a molecular spiral-staircase, enters this class. Planarity is prevented by the presence of two pairs of carbon atoms which, in a planar arrangement, would occupy the same position. The optical rotation of this molecule, so strongly distorted, is enormous: a full 3600 degrees expressed according to the normal convention. Thus optically active compounds can be obtained in the absence of asymmetric atoms of the classical type.

The picture is now complete. The compounds of nitrogen, phosphorus, sulphur and also some metals of high valency may be treated in a manner analogous to those of carbon. We have tried to give an account sufficient to explain the most varied and complex molecules. But, above all, we hope to have given the criteria required to make sense of the different phenomena. We also hope we have made clear the necessity and the usefulness of a formal treatment, even if reduced to a short account.

Symmetry is an important and complex subject in the study of matter generally and not simply in its application to problems of optical activity. Spectroscopic properties, as well as chemical reactivity and biological action, are strictly related to it. At a more profound level, the laws that govern the formation and the breaking of chemical bonds are regulated by general principles of symmetry. A detailed treatment of this matter has been evolved by theoretical chemists and, at the present moment, is beginning to influence the most diverse groups of experimental chemists.

V

Some aspects of reaction dynamics

The study of molecular shape and symmetry which was developed in the preceding chapter constitutes the so-called structural or static stereochemistry. This term immediately suggests the existence of another stereochemistry – which we shall call dynamic – directed to the study of molecular transformations. The problem can be expressed in these terms: what happens when the time in addition to the usual x, y and z spatial co-ordinates, is introduced into the examination of molecular structures? We have partially covered this when dealing with conformational analysis and the symmetry properties of flexible molecules. But we now wish to illustrate other aspects of the movement of molecules: those connected with a substantial modification of their structure.

When a compound A is transformed into B, what remains of its original structure? Does memory play a part in chemical reactions? And if it exists, how is it transmitted and how does it work? There are obviously great implications hidden in these questions and the significance they can have both on the synthetic and the practical plane and in connection with a knowledge of chemical and biological mechanisms.

The chemist is a molecular architect. We shall try to give substance to this image by searching for the rules which govern reactions, so as to see how it may be possible to construct molecules according to a predetermined plan.

Chemical reactions may be grouped into four fundamental types: addition, elimination, substitution and rearrangement (Fig. 58). Even if the significance of these terms is quite clear by themselves, it will be useful for us to dwell a moment on these definitions.

The formation of a molecule by the union of two others constitutes an addition process; a typical example is the addition of chlorine or bromine to unsaturated molecules. The compound obtained by addition is sometimes called an adduct, especially when it has low stability and can easily be reconverted into its components.

An elimination (or decomposition) process occurs when a molecule is split into other simpler ones, as in the reaction of dehydrochlorination of a chloroparaffin which leads to the formation of hydrogen chloride and an unsaturated compound.

The substitution (or displacement) reaction consists in detaching part of the molecule and replacing it with a particular atom or group of atoms. As an example, we may mention the preparation of alcohols from organic halides. Owing to their relatively simple nature substitution reactions are widely studied from kinetic and stereochemical angles and we shall be dealing with them in more detail later.

Finally, there are molecular rearrangement and isomerization reactions which involve a movement of atoms or groups of atoms within the molecule, and which give rise to a more or less profound change in its structure.

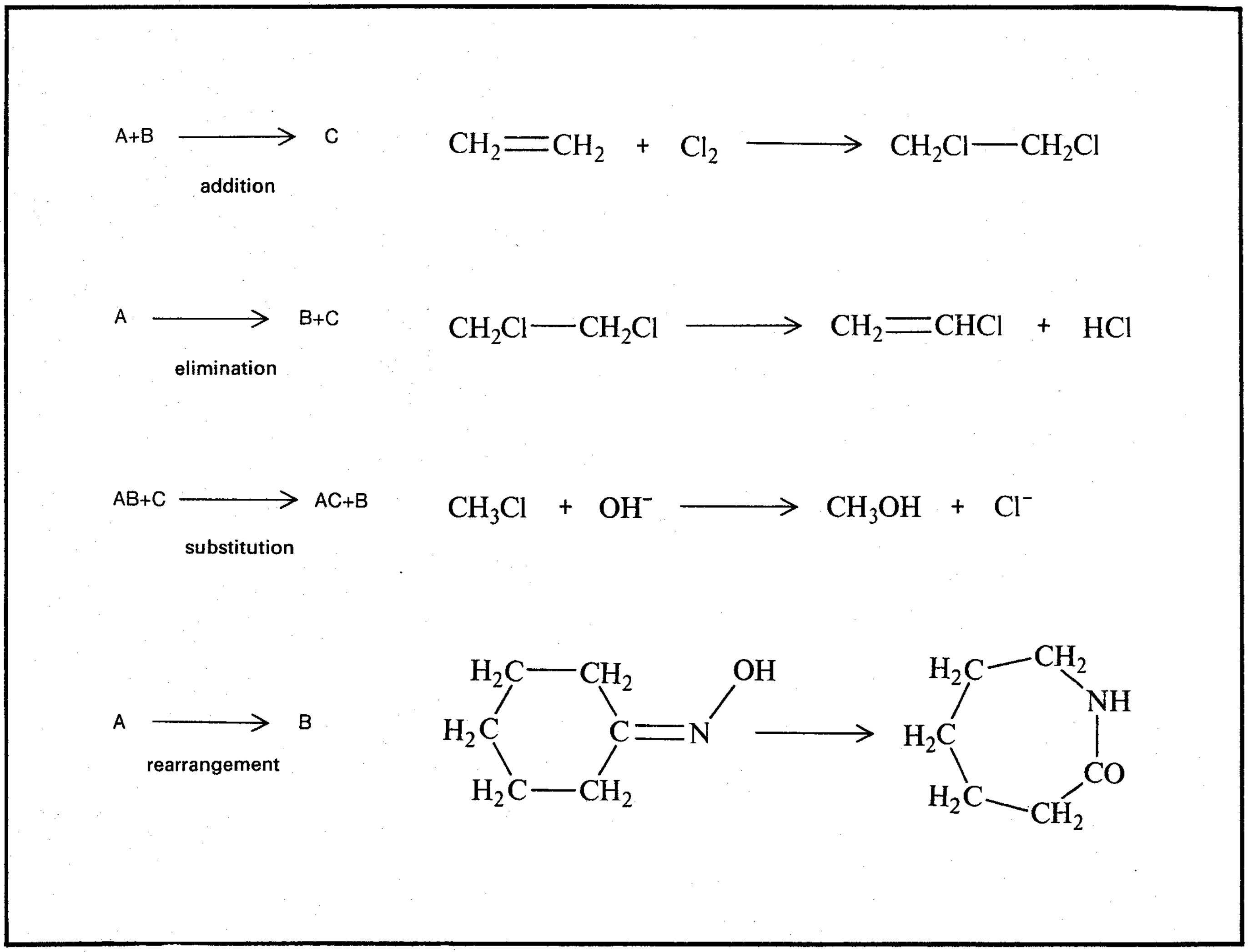


Fig. 58 **The four fundamental types of chemical reaction. From the top: chlorination of ethylene, with the formation of dichloroethane (addition reaction); dehydrochlorination of dichloroethane and formation of vinyl chloride (elimination); reaction between methyl chloride and the hydroxyl ion to give methyl alcohol (substitution); and finally a Beckmann rearrangement, the conversion of the oxime of cyclohexanone into caprolactam.**

A particular chemical process generally consists of several stages, each one of which can be associated with one of these four classes of reaction. For instance, in the industrial process for the synthesis of vinyl chloride, the primary material in the manufacture of many plastic materials (PVC and vinyl leathers, for example, all being derived from vinyl chloride), there is first the *addition* of chlorine to ethylene to form dichloroethane, followed by the *elimination* of hydrochloric acid and the formation of monochloroethylene (vinyl chloride) (Fig. 58).

But passing beyond these formal definitions, the study of chemical reactivity requires consideration of the balance of the matter and energy which are involved in the reaction.

The driving force of chemical reactions

The first parameter which must be taken into consideration in the study of molecular transformations is the stoichiometry of the reaction, or the molecular ratios of all the chemical compounds concerned, reagents and products. A typical chemical reaction is represented by an equation giving the formulae of all the interacting chemical species which are each accompanied by a coefficient

CH_4	+	Cl_2	$\longrightarrow$	CH_3Cl	+	HCl
16		71		50,5		36,5
CH_4	+	$2Cl_2$	$\longrightarrow$	CH_2Cl_2	+	2HCl
16		142		85		73
CH_4	+	$3Cl_2$	$\longrightarrow$	$CHCl_3$	+	3HCl
16		213		119,5		109,5
CH_4	+	$4Cl_2$	$\longrightarrow$	CCl_4	+	4HCl
16		284		154		146

Fig. 59 The balanced equations of some reactions. The numbers in front of the formulae indicate the relative number of molecules which react and are produced; the numbers below are proportional to the weights of the reagents and products. It can be seen that the sum of the weights of the reagents is equal to that of the products in agreement with Lavoisier's law.

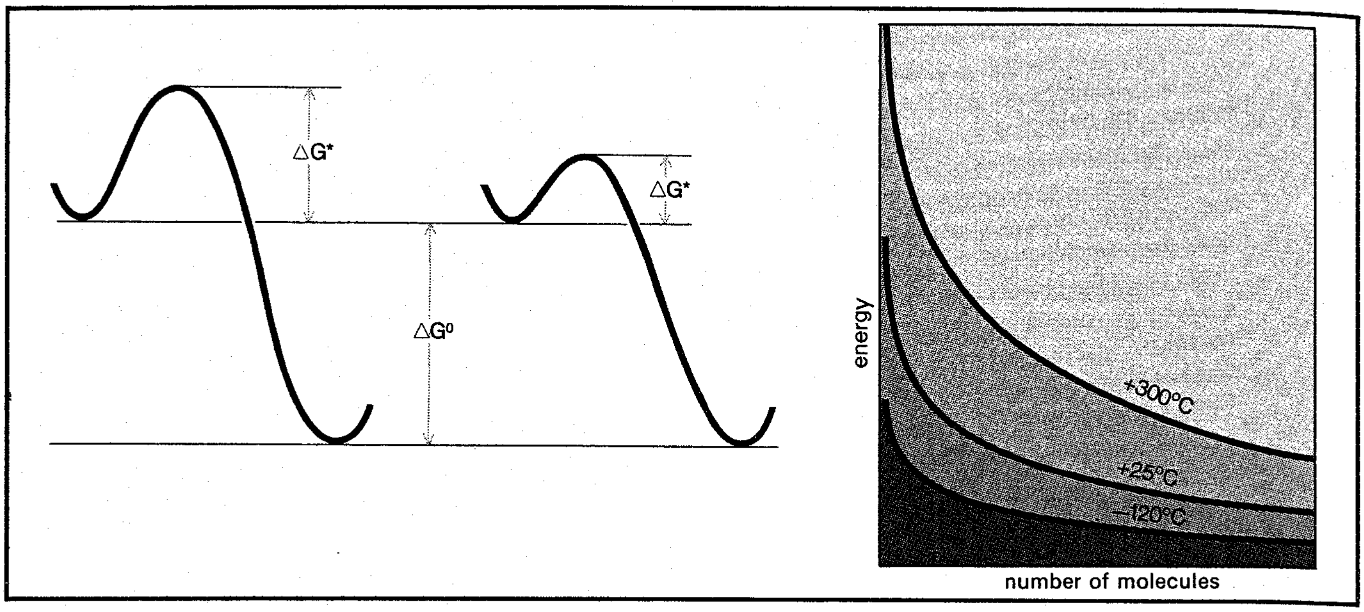


Fig. 60 **A chemical reaction can only take place if the free energy of the final state is lower than that of the initial one. But kinetic considerations (relative to the rate of reaction) often limit this thermodynamic law. If the activation energy is high, the reaction proceeds slowly. However, if the height of the barrier can be reduced (for example, by using a catalyst), the rate increases, sometimes by many orders of magnitude. An increase in the temperature also generally favours a rapid reaction. At a higher temperature there is a greater number of molecules with sufficient energy to overcome the energy barrier; this may be seen in the diagram on the right.**

defining the relative number of molecules taking part in the reaction (Fig. 59). For every mole of a compound to disappear a certain number of moles of different products are formed in such a manner that the total weight of reagents and products remains constant. This balance can be verified both when the reaction is finished (i.e., completely shifted to the right), or when it is stopped at an intermediate point.

As we shall see in more detail later, the completion of a reaction takes a certain time since the rate of molecular transformations is not infinite. It is thus possible to interrupt the reaction at a certain desired stage. In addition there are many reactions which do not go to completion even after a long time. In these cases a dynamic equilibrium between the reagents and products is set up. The starting molecules are converted into the products but these in their turn are reconverted to the first type. Equilibrium is reached when the rates of the forward and reverse reactions are equal.

The factor which regulates the position of chemical equilibrium and generally forces the molecule to react and be transformed into other molecules is of an energetic nature. A simple analogy illustrates this. A water reservoir or a lake high up in the mountains represents an energy store of great value. If there were no obstacles (mountains, embankments or dams) the water would flow down to the valley in order to reach a position of lower energy, where it would be more stable. Every river tends to flow towards the sea. This observation can be translated into chemical terms in the following way: the driving force of chemical processes consists of the general tendency of any system to reduce its energy, giving the excess in various forms to the surroundings (Fig. 60). The energy developed in chemical reactions can be very large and represents the most important source of heat and energy known to man. It is sufficient to think of all the processes of combustion, from automobile engines to thermoelectric power stations, to see how modern life is based directly upon the energy of chemical reactions. The great sources of mechanical or thermal energy obtained by way of chemistry – coal, oil and natural gas – are still in general more important than their rivals, hydroelectric, solar, geothermic and nuclear energy, and it is expected that they will continue to be so for many years to come.

It is, however, important to state clearly that the force which directs chemical reactions does not coincide with the heat developed by the reaction but is expressed more correctly as Gibbs energy or free energy, a thermodynamic function involving enthalpy, the absolute temperature and the entropy. Without discussing the exact definitions of these quantities, it is sufficient to say that the enthalpy, to a first approximation, is related to the presence of chemical bonds and the forces between atoms, entropy can be associated with the notions of order and disorder, while the temperature is an index of the degree of agitation of a system (translational velocities of the molecules, amplitudes of vibration, etc.). The variation of enthalpy coincides with the heat of reaction and is negative for exothermic reactions (which produce heat) and positive for endothermic reactions. The entropy of a compound has a positive value which is greater the higher the temperature and the more disordered the molecular system. For example, water vapour has more entropy than liquid water which in turn has more than ice. In a reaction the entropy variation is positive if the system evolves towards a situation of greater disorder. The symbols normally used for these quantities are ΔG, ΔH and ΔS for, respectively, the changes in free energy, enthalpy and entropy. The relationship between the three quantities is $\Delta G = \Delta H - T\Delta S$, where T is the absolute temperature. In some texts the symbol G is replaced by F.

A chemical system can transform spontaneously into another when the free energy of the final state is less than the initial, i.e., when ΔG (the difference between the Gibbs energies of the final and initial states) is negative ($\Delta G < O$). In the course of the reaction this difference diminishes and a point is reached in which it becomes zero ($\Delta G = O$); we are then at a state of equilibrium in which the reagents and products of the reaction coexist.

Reaction rates and mechanisms

Having determined the conditions necessary for reactions to take place, we may then ask if reactions actually occur in all the cases in which a change in the system produces a reduction of free energy. Our reply is definitely negative. If the stability of a compound or a mixture of compounds was determined only by thermodynamic factors, these pages could not be written. Life would not in fact be possible, at least in the form developed on Earth. For living organisms to occur, an enormous series of extremely delicate and unstable compounds is necessary (proteins, nucleic acids, enzymes, etc.) while thermodynamics tells us that in the presence of oxygen no organic compound is stable, except as its combustion products (carbon dioxide, water, etc.).

The comparison with water levels again comes to our aid. Although the sea is found at a lower level than an alpine lake, the water of the latter is prevented from flowing down by mountains and dams. However, if we could force some water over the dam for example by producing waves, then nothing more would oppose its downward fall. We can also imagine something similar for molecules. A mixture of the two gases, hydrogen and oxygen, is thermodynamically unstable; at room temperature and above the stable chemical system consisting of hydrogen and oxygen atoms is water. Yet hydrogen and oxygen will not react unless they are at a high temperature – i.e., until they are lit with a flame – or unless a catalyst is present, for example, a trace of platinum or palladium powder. (We do not suggest you try this experiment. Hydrogen and oxygen combine in a very fast or explosive way which can be extremely dangerous!) The non-reactivity of the hydrogen-oxygen mixture is attributed to the presence of energy barriers – analogous to the dams in our hydraulic example – which must be overcome before reaction may occur.

The two methods of igniting the hydrogen-oxygen mixture, heating or the use of a catalyst, correspond to two different ways of overcoming the hydraulic barrier: to increasing the height of the waves or to lowering the level of the wall of the dam (Fig. 60).

The kinetic theory of gases tells us that the average energy of a system does not coincide with the energy of each single particle. A certain number of molecules possess an energy greater than the average and this fraction is greater the higher the temperature. One thus understands why the reaction rate grows with temperature in almost all cases: what is impossible or very unlikely at low temperature can occur easily at higher temperatures where the molecular wave, to continue the metaphor, is higher and thicker.

The relationship between temperature and reaction rate is one of

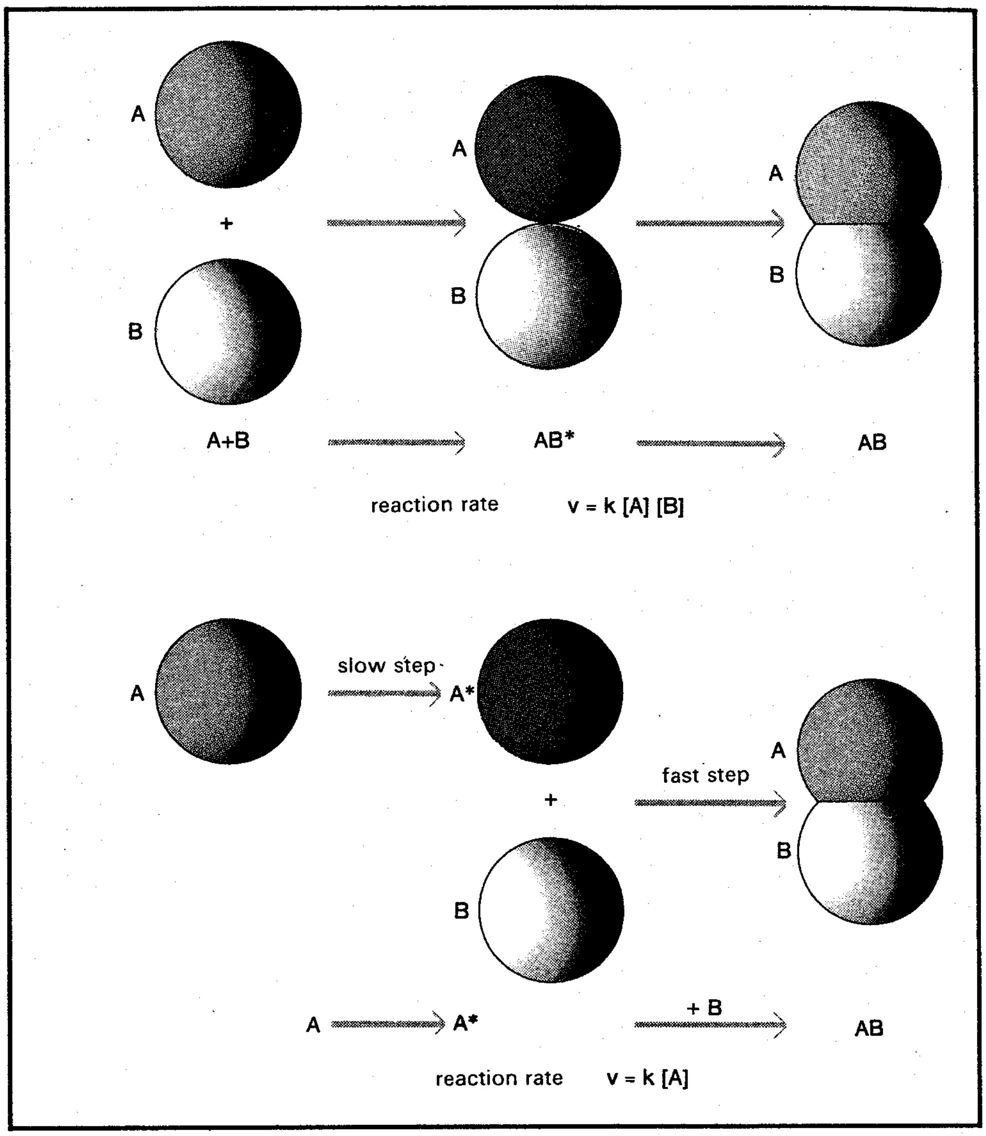


Fig. 61 Illustrations of bimolecular and unimolecular mechanisms for reactions between A and B. In the bimolecular mechanism an activated complex AB* is first formed; this is rapidly transformed into the compound AB (above). Below: in the unimolecular reaction, the reagent A is first converted into the activated species A* which then reacts with B to give the final product.

the most interesting topics of chemical kinetics but the study of reaction mechanisms presents other aspects no less important. Suppose we have two compounds A and B whose reaction produces one new compound, C, followed by, a second, D. If one tries to explain the rate of this reaction in mathematical terms the concentrations of the reagents must be introduced as parameters in the equation. The rate is generally higher the greater the concentration of A or B or both. A series of equations of varying complexity relates the yield of the products of a reaction, or its situation at a given time, to the different factors affecting the system (time, temperature, concentration or pressure of the individual reagents etc.).

A knowledge of the kinetic behaviour of a reaction is often of the greatest usefulness. The economic viability of an industrial process can often depend on being able either to raise the yield by 5 or 10 per cent, or to reduce the reaction time, or else to lower the temperature when the working conditions of a plant are particularly troublesome.

However, further useful information may be obtained. A knowledge of the factors on which the speed of a reaction depends suggests a possession of some essential information for the interpretation of its mechanism at the molecular level. When the speed of a reaction between A and B depends on the concentration of both A and B we may suppose that the determining factor must be a collision between a molecule of A and a molecule of B. The probability of such an event is proportional to the number of molecules of A and B present in a certain volume. A reaction mechanism can then be formulated in which the rate-determining step is just an efficient collision between a molecule of each sort (Fig. 61).

The number of molecules on which the speed of a reaction depends, the so-called order of a reaction, does not necessarily coincide with the stoichiometric coefficients discussed above and, in most cases, there is no obvious relationship between the two numbers. A chemical reaction really consists of a successive series of simple events each occurring with its own speed, different from that of the others. The speed of the complex process coincides in practice with that of the slowest step. This phenomenon is well known and is also true in other areas: the maximum traffic on a toll road or turnpike, the exit from a stadium or a cinema, are strictly regulated by the slowest event, which consists of the payment of the toll or of the passage through the turnstiles or the doors.

Even if the only kinetic knowledge available is limited to the slowest step of a reaction, the information which may be derived is still quite useful. Let us return to the reaction between A and B: if its rate depends only on the concentration of A (rather than of both A and B), the mechanism must be radically difficult from that considered above. It no longer concerns a collision between A and B – at least this is not a decisive factor in the kinetics – but one can suggests a slow transformation of A into an intermediate species, A*, followed by a rapid reaction of A* with B to give the products,

The kinetic interpretation of a reaction is of fundamental importance for describing the mechanism correctly. But it is important to note that if it is not integrated with other methods, if it is not given a chemical content, the study of kinetics risks remaining a purely mathematical exercise. From this point of view one of the most efficient aids to kinetics is stereochemistry. We thus return to our principal topic.

How molecules are modified

Suppose that we break a molecule into simpler fragments or subject it to a series of transformations to convert it into a more complex product: what relationship exists between the reaction products and the starting compound?

One of the guiding principles in the determination of organic molecular structures is the so-called principle of minimum structural variation. Reaction products, apart from the particular case of rearrangement reactions, are considered to have the same basic structure as the starting compound, the variations being confined solely to the point at which the molecule reacts. The widest use of this principle has been made and is still made in determining molecular structures. It is amply justified by the great amount of experimental confirmation obtained and also by independent chemical-physical studies. But even the purely chemical data obtained forms a perfectly coherent picture.

A chemist appears here like a person ardently devoted to solving riddles, at grips with a difficult crossword: an initial hypothesis, a correct word permitting new solutions which in their turn confirm the hypothesis until the whole is given a complete internal consistency. The more complex the crossword the greater is the probability that the solution is correct. Precisely this great number of intersecting points and internal confirmations has given the principle of minimum structural variation its great authority. One would even be tempted to consider it a principle of general validity and to explain it in the following way: in the course of a reaction the bonds of a molecule which break reform in a manner substantially the same as in the original molecule. In the form in which we have now stated it, however, the principle is wrong or at least cannot be generally sustained.

Without placing doubt on the usefulness of the principle of minimum variation it is necessary to state exactly its area of applicability, by presenting all the favourable and unfavourable facts. These have been known ever since Paul Walden discovered those processes which bear his name. We shall describe one example in some detail (Fig. 62).

Chlorosuccinic acid is an asymmetric compound which can exist in optical antipodes; we shall consider only one, the negative form. (−)-chlorosuccinic acid can be converted by the action of two different reagents into (+) and (−) malic acid respectively. The Walden cycle is further complicated since each of the two malic acids can be converted again into either (+) or (−) chlorosuccinic acid with a further change of sign. The whole system of reactions can be repeated by starting from (+)-chlorosuccinic acid.

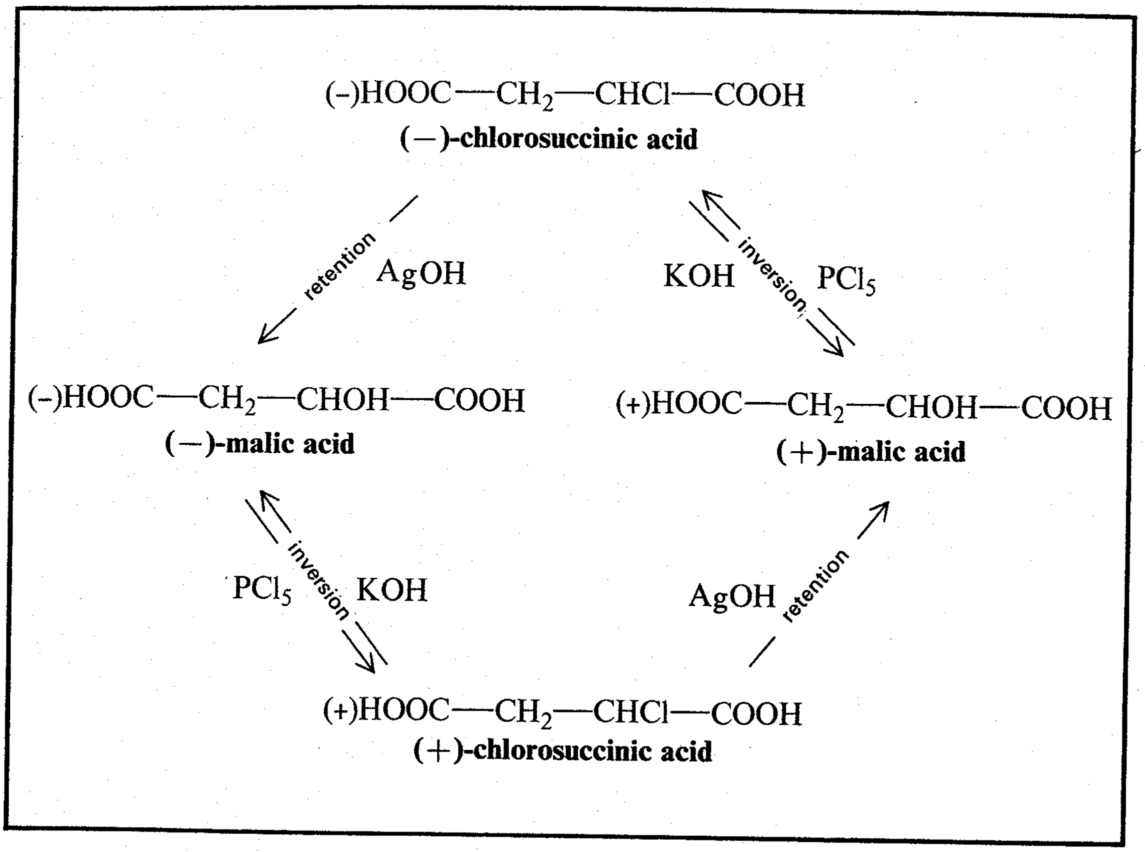


Fig. 62 In the conversion of malic acid into chlorosuccinic acid, and vice versa, numerous Walden inversions (i.e., inversions of configuration) occur. Reactions that take place with retention of configuration are much rarer than those which lead to inversion.

Even if we do not know the relationships between the sign of optical rotation and the configuration for the compounds in question (we have already said that this correlation is not easily determined), we can say with certainty that in some of these reactions there is an inversion of configuration – a single enantiomorph has been converted in two reactions into a pair of antipodes. The formulation given above for the principle of minimum variation is therefore not valid since it is clear in this case that the bond is not reformed in an unaltered form, i.e., in the same position with respect to the other substituents.

Originally considered as curiosities, the phenomena connected with the Walden inversion are today considered the rule and not the exception. This is a good example of the sensitivity of stereochemical methods and their ability to enquire into the intimate mechanism of reactions. The existence of an inversion of configuration can only be observed by working with optically active compounds because whatever the steric mechanism (retention, inversion, racemization), a racemic compound is always converted into other racemic compounds. There is, however, an exception to this statement provided by those compounds which contain two or more asymmetric carbon atoms. (The possibility of observing the Walden inversion in racemic compounds also depends in this case on the existence inside the molecule of other asymmetric atoms whose configurations remain unaltered and which constitute an element of constant reference.) The results obtained from optically active compounds can be legitimately transferred to compounds which are not dissymmetric. In the case of the latter the same results may be demonstrated by isotopic methods and the general validity of the conclusions may be arrived at.

Around 1930 Sir Christopher Ingold made a decisive advance in the interpretation of reaction mechanisms: he succeeded in combining within a single hypothesis both the kinetic and the stereochemical behaviour of substitution reactions. In particular, he studied nucleophilic substitutions, those in which both the leaving and incoming groups are especially rich in electrons. From the kinetic point of view such reactions can be of first or second order, depending on whether their rate depends on the concentration of a single organic compound (also called a substrate) or on those of the substrate and reactive nucleophile (the substituting agent) together. From the stereochemical point of view these reactions can be further divided into those which occur with racemization and those which occur with inversion of configuration (the retention of configuration is rarely observed).

The great discovery of Ingold was that a well-defined steric behaviour corresponds to each type of kinetic behaviour and that the two radically different phenomena, optical activity and reaction rate, can be explained on the basis of the same reaction mechanism.

We have already briefly described the mechanisms by which a reaction between A and B can display kinetic behaviour of first or second order. We shall now describe them precisely for the specific case of substitution reactions. From now on we shall use Ingold's terminology, according to which they are called respectively S_N1 and S_N2 reactions; the number indicates the order of the reaction and the letters signify nucleophilic substitution.

Let us consider an exchange reaction between the substrate AX and the nucleophilic agent Y. The products of the reaction will be AY and X. We say that the reaction is of the S_N1 type if its rate depends only on the concentration of AX. In the S_N1 reactions there is generally a racemization of the substrate. If one starts from the optically active compound AX, the product AY is obtained in an inactive form or, at least, with an optical purity much lower than that of AX. If, on the other hand, the reaction runs according to the S_N2 scheme the reaction rate depends on the concentration of both AX and Y. In this case there is usually an inversion of the steric configuration of the substrate; it passes, for example, from the D to the L series if referred to a standard compound like D-glyceraldehyde

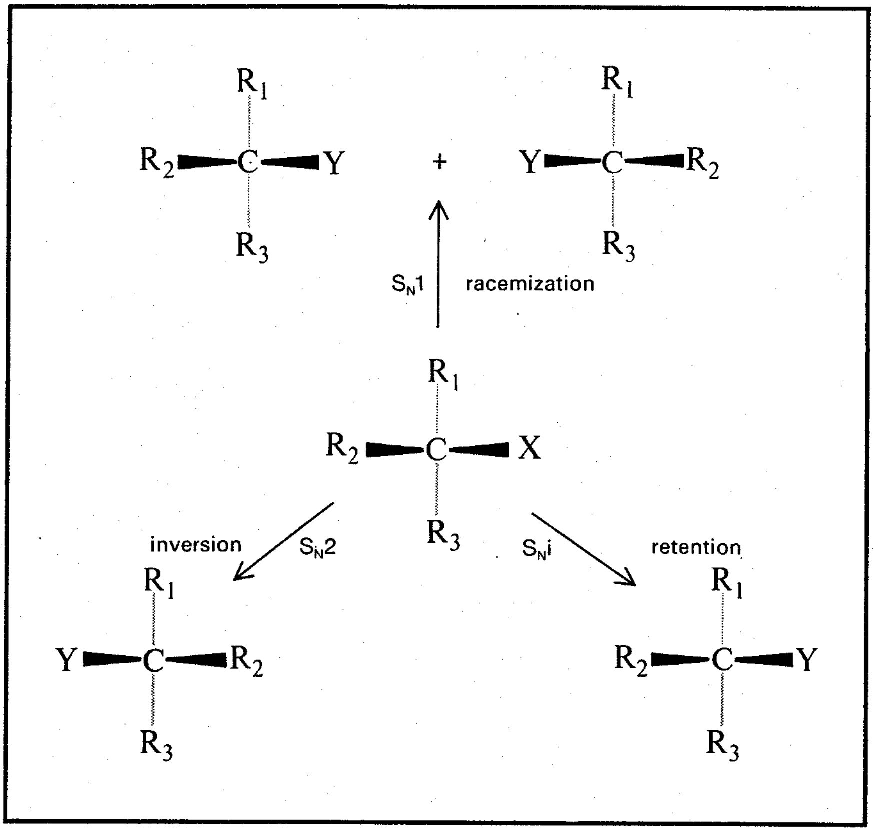


Fig. 63 The steric route of S_N1 and S_N2 reactions. These lead respectively to racemization and inversion of configuration. Other less common substitution reactions which take place with retention of configuration are the S_Ni or internal nucleophilic substitutions.

(Fig. 63). The kinetic and steric behaviour of an S_N1 reaction was explained by assuming that the reaction takes place in two successive phases. In the first place the compound AX eliminates the group X generally as an anion X^-, and is transformed into a positive ion, A^+. This phase is relatively slow and thus determines the kinetic order of the whole reaction. The A^+ ion comprises a carbon atom bonded to only three substituents and is positively charged (a *carbenium ion*); it has a planar, triangular shape and possesses a plane of symmetry. Even though the AX compound was optically

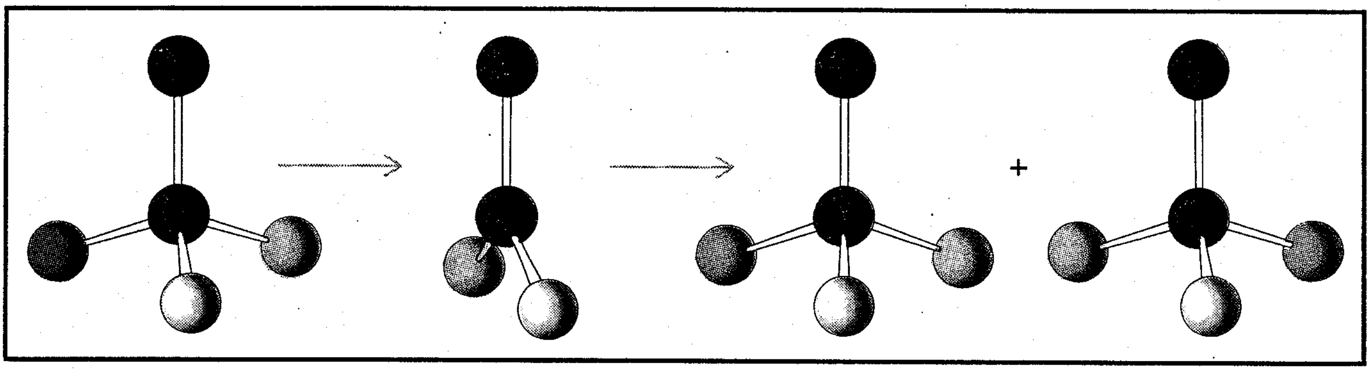


Fig. 64 The substitution reaction $AX + Y^- = AY + X^-$ is called S_N1 when it follows a first order kinetic equation ($v = K[A]$). The activated species consists of a positive carbenium ion produced by the elimination of X^+. The planosymmetric structure of the carbenium ion ensures that the attack of the reagent Y^- occurs with equal probability on the two opposite faces, leading to the formation of an equal number of antipodal molecules.

active, the transition state A$^+$ is obviously symmetrical (at least in as far as ionization is complete and there are no other interactions); consequently, the product of the reaction can no longer be asymmetric. In the second phase the nucleophile Y reacts with equal probability on either side of the symmetry plane of the ion A$^+$ to give a racemic mixture of laevo and dextro AY molecules (Fig. 64).

In S_N2 reactions, however, the transition state most probably consists of an unstable negative ion of the type (YAX)$^-$ in which the carbon atom is surrounded by five neighbours. It has the form of a trigonal bipyramid with the two nucleophiles placed at opposite vertices. A transition state of this kind leads to second order kinetics (the rate depends on the number of efficient collisions between AX and Y) and to steric inversion (Fig. 65). The fact that the nucleophile Y approaches the molecule on the opposite side from X is fully justified on electrostatic grounds. The two nucleophiles repel each other since both are rich in electrons and therefore have the same electric charge.

This type of interpretation was the starting point of modern physical organic chemistry, the science that studies reaction mechanisms in all their aspects, and it remains today one of its most important successes. Since Ingold's time, however, further advances have been made. What is the effect of the solvent or the addition of other substances? How can one explain the partial racemization of certain S_N2 reactions or the partial inversion which is observed in S_N1 reactions? What happens when a molecule has more than one reactive point?

The S_N1 and S_N2 schemes should be considered as model reactions, to some extent extreme cases, while many reactions have an intermediate behaviour with partial inversion and partial racemization. For this intermediate area, for the so-called *borderline* reactions,

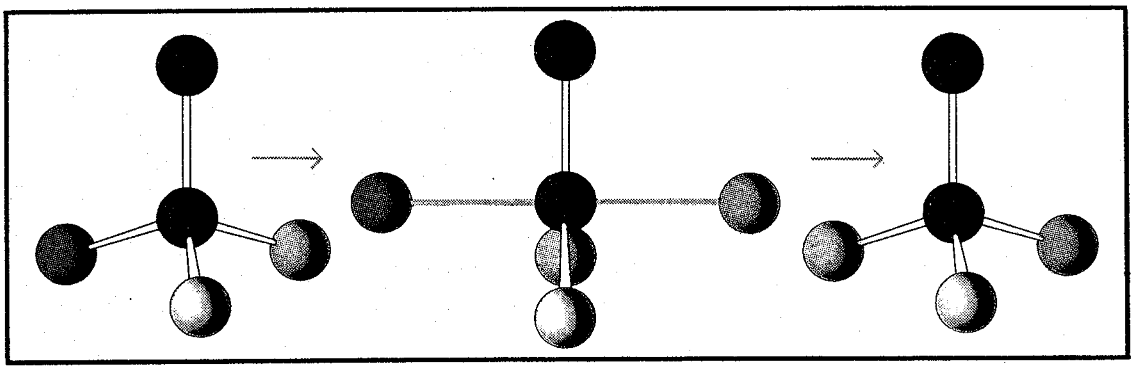


Fig. 65 The substitution reaction AX + Y$^-$ = AY + X$^-$ is instead called S_N2 when it follows second order kinetics (v = K[A][Y$^-$]). The active species consist of a complex (YAX)$^-$ with the form of a trigonal bipyramid having the nucleophilic agent and the leaving group on opposite sides to each other. The reaction product AY has a configuration opposite to that of AX because the entering group approaches from the side opposite to that of X.

there are different interpretations. In some cases, and according to some scientists, borderline reactions show an effectively intermediate mechanism (incomplete elimination of X in the transition state, formation of ion-pairs, etc.); in other cases and according to other researchers they show the superposition of two simultaneous reactions, one being S_N1 and the other S_N2. In cases of this type the paradoxical result is often obtained that the use of concentrated reagents, conditions traditionally considered very drastic, produces a cleaner reaction from a steric point of view. This arises from the different relationship between inversion (the S_N2 reaction being proportional to the concentration of the nucleophilic agent) and racemization (S_N1 reaction independent of Y). Increasing the concentration of Y raises the contribution of the S_N2 reaction with respect to the S_N1.

Stereospecific reactions

It is well known that organic compounds containing double or triple bonds (for example, those containing the groups C=C, C≡C, C=O, C≡N, etc.) are highly reactive and tend to be easily saturated.

A chemical system formed from single bonds is generally more stable than a system containing double or triple bonds; it arises from the lower energy of σ bonds compared with π bonds.

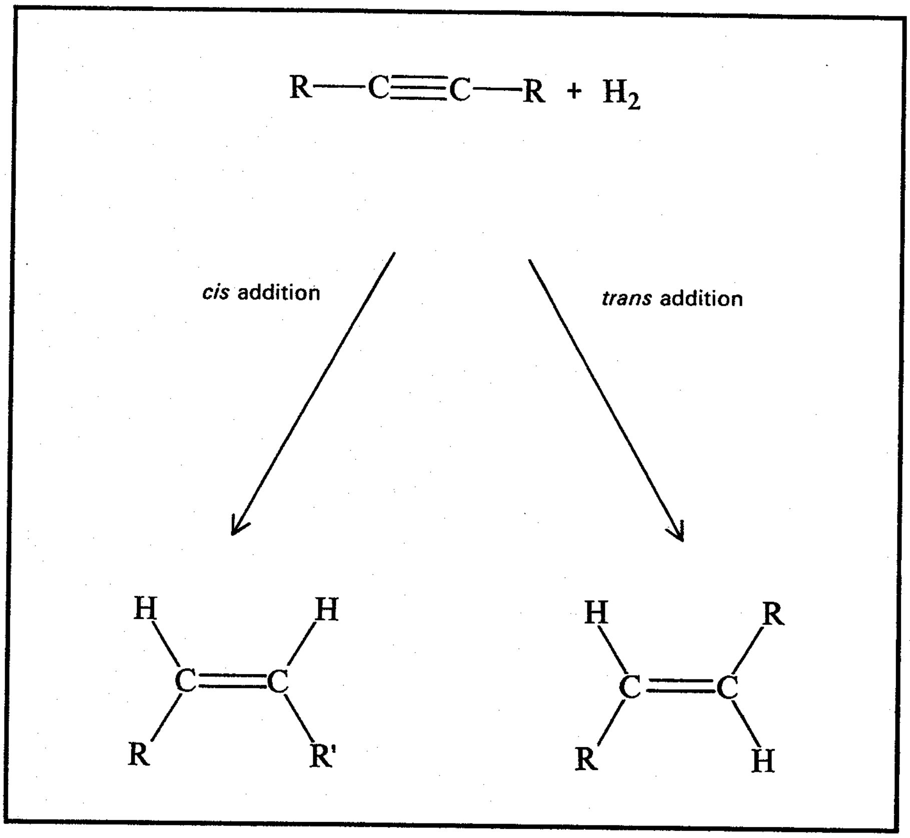


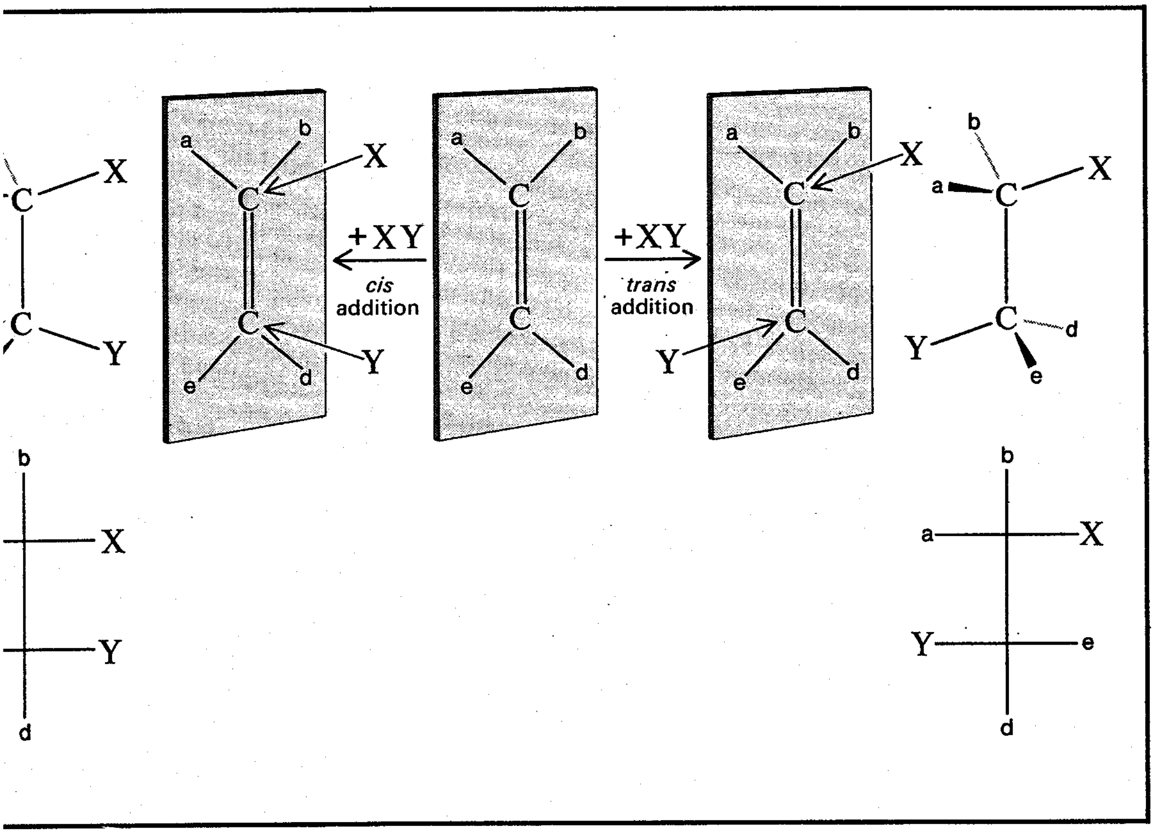
Fig. 66 An addition to an acetylenic compound is called *cis* (or *trans*) when the two atoms introduced into the molecule are in *cis* (or *trans*) positions with respect to the double bond.

Fig. 67 An addition to an olefinic compound is called *cis* when the two atoms add from the same side of the plane defined by the four atoms adjoining the double bond; it is called *trans* when the two atoms add from opposite sides of such a plane. The *cis* and *trans* additions lead to compounds which are diastereoisomers of each other, as can be seen from their Fischer projections. Note that if the direction of approach of X and Y is from the other side of the plane in both *cis* and *trans* addition, the enantiomorphs of each of the two diastereoisomers will be obtained. This normally occurs and leads to racemic mixtures.

From the kinetic point of view, also, addition reactions quite often take place readily, having activation energies which are relatively low. Given the abundance of electrons in multiple bonds, addition reactions are more often of an electrophilic than of a nucleophilic nature, in the sense that with a reagent of the type XY the atom or group with the lower electron density reacts first and is next followed by its 'partner'. The stereochemical implications which we now wish to discuss are independent, however, of the exact electronic mechanism since they are based solely on the structural relationships between starting compounds and reaction products.

The simplest example of the stereochemistry of addition reactions is the partial hydrogenation of acetylenic compounds. In this reaction, a linear compound containing a triple bond is converted to a compound of the olefine series having a double bond and a planar structure. As we have already said in chapter III, these compounds can exist in two isomeric forms (also called geometrical isomers), one of a *cis* type and the other a *trans*. Experimentally, starting from a disubstituted acetylene and by suitable variation of the conditions of hydrogenation (such as temperature or pressure), either the *cis* or the *trans* isomer can be obtained. The two processes are called, respectively, *cis* and *trans* addition processes (Fig. 66).

In considering the stereochemistry of additions to olefines, it is necessary to deal further with the significance of the terms *cis* and *trans* addition. In an olefinic compound the two unsaturated carbon



atoms and the four immediately adjacent atoms lie in a plane. We then define a *cis* type of addition as that in which the two new valencies are formed on the same side of the plane. By contrast, addition of the *trans* type occurs when the new bonds form on opposite sides of the plane (Fig. 67). To eliminate too frequent use of the terms *cis* and *trans*, a proposal has recently been made to replace them by suprafacial *(cis)* and antarafacial *(trans)*.

Both types of addition are possible. Whenever a certain reagent adds in only one way, *cis* or *trans*, the reaction is called *stereospecific* or *stereoselective*. (There is a certain disagreement between various authors on the use of these terms; but we consider that an exact distinction on this matter is for the specialist). Epoxidation, and hydroxylation with permanganate or with osmium tetroxide are specific reactions of the *cis* type. *Trans* hydroxylation of olefines is possible by using peracids. The hydroxylation reaction of olefines is particularly interesting since it can be conducted in either a *cis* or *trans* manner depending on the reagent employed; by starting from two different unsaturated isomers it is possible to describe a cycle of reactions analogous to the Walden cycle (Fig. 68). An explanation for this phenomenon is as follows. Both in the permanganate and peracid cases, a cyclic compound, with five atoms in the first case and three in the second, is first formed by *cis* addition. The subsequent decomposition of the intermediate compound necessarily requires the breakage of a carbon-oxygen bond by an S_N2 reaction with consequent inversion of configuration. In the permanganate case, however, the formation of the glycol occurs without inversion since the bonds which break in the second phase of the reaction are those between oxygen and the metal and not between oxygen and carbon (Fig. 69).

The explanation of *trans* addition in the bromination reaction is quite analogous (Fig. 70). The transition state consists of a cyclic bromonium ion which is obtained by the *cis* addition of a bromine cation to the double bond. The second bromine atom, in the form of a negative ion, adds from the side of the three-atom ring opposite to the first bromine with consequent inversion of configuration at the carbon atom. A confirmation of this two-stage mechanism lies in the observation that the presence in solution of high concentrations of other anions, such as chloride ion, leads to the formation of mixed (chloro-bromo) compounds rather than the dibromo adduct.

Addition and substitution reactions are not the only ones to proceed stereoselectively, i.e., with very precise steric requirements *Trans* eliminations are quite usual examples in which the two fragments which break off from the molecule – in the transition from a saturated to an unsaturated compound – assume an *anti* or *trans* (at 180°) conformation in the transition state. There are also some

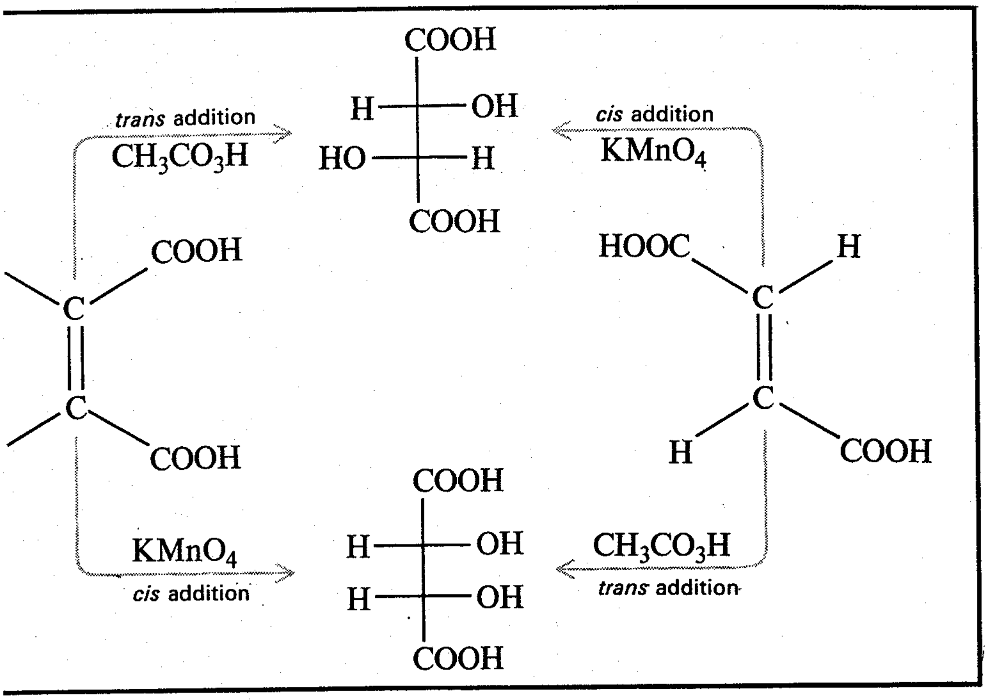


Fig. 68 By *cis* hydroxylation with permanganate ($KMnO_4$) *meso*-tartaric acid is obtained from maleic acid (below) while *trans* hydroxylation of the same compound with peracetic acid gives racemic tartaric acid (above). The action of the same reagents on fumaric acid (on the right) leads to the racemic acid and to *meso*-tartaric acid respectively.

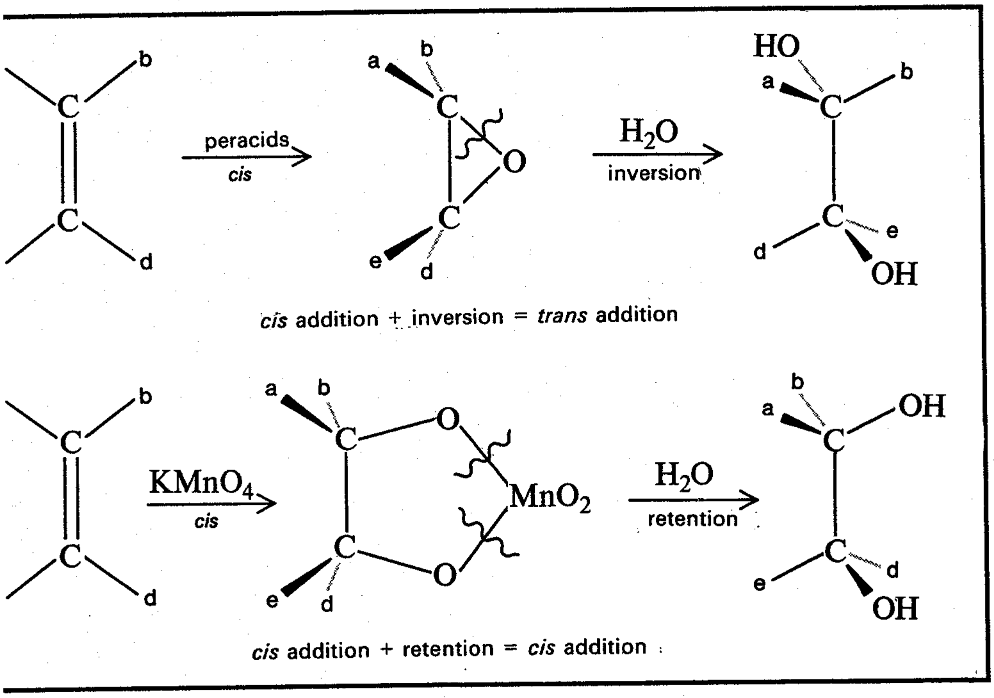


Fig. 69 The final result of a reaction often does not correspond to the first stage. Above, there is first a *cis* addition of the oxygen to the double bond to form an epoxide; the addition of water takes place with inversion of configuration and the final result is *trans*. Below, the passage from the five-membered intermediate to the glycol does not involve the carbon-oxygen bonds and thus does not alter the configuration.

rearrangement reactions with retention of configuration, such as the Hofmann degradation which converts amides to amines and which can be used for the determination of the absolute configuration of optically active acids.

At this point we may ask ourselves what causes the different steric behaviour of different reactions. Among the possible factors, the structure of the transition state probably plays the dominant part. Rigorously, one should speak of the structure of the activated complex, that particular aggregate of atoms which corresponds to the transition state, or to the maximum on the energy curve. (The transition state is strictly an energetic concept, but the two terms are

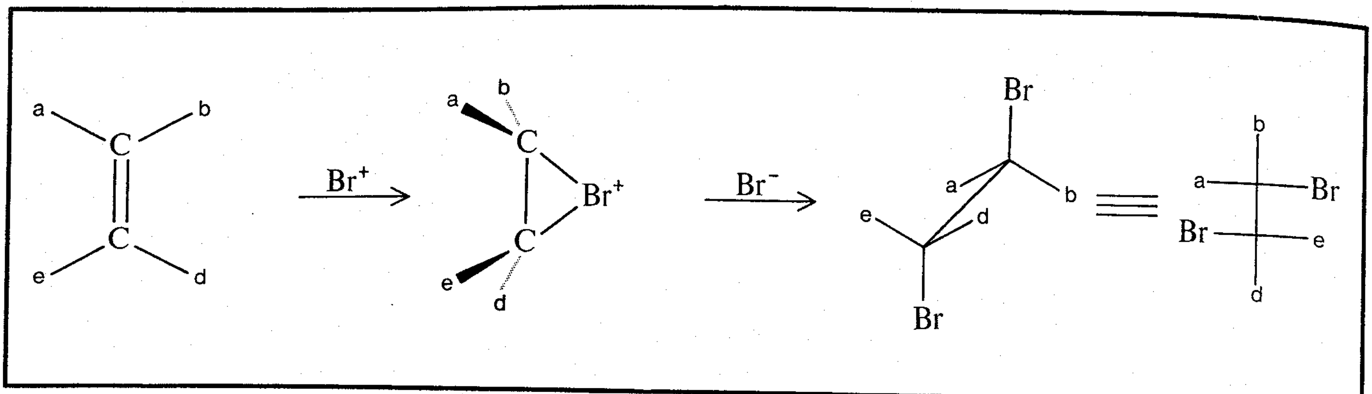


Fig. 70 **The addition of two bromine atoms to an olefine occurs in two stages. Firstly, an attack by the Br^+ cation produces a three-membered cyclic compound called the bromonium ion. Br^- then adds from the side away from the ring causing an inversion of the configuration at carbon. The complete reaction thus takes place with a *trans* mechanism.**

often used synonymously.) We have already seen that the geometry of the carbenium ion in S_N1 substitutions is planosymmetric and the reactive nucleophile can approach in an identical manner to either face of the planar ion. The reaction is thus to no extent stereospecific. The further one moves from this extreme case, the greater will be the selectivity of the reaction. For instance, a reaction which does not proceed through totally free ions or, better still, which maintains a certain degree of covalency in the bonds that are breaking or being formed, can be highly stereospecific, for example, S_N2 substitutions or reactions which occur with the assistance of neighbouring groups.

Here is a possible aid for the chemist. By choosing his reagents, catalysts, solvents, temperature and so on, he can select the most suitable conditions for achieving a given stereochemical course. If he wishes to carry out a reaction in a highly stereospecific manner, the reaction must be one in which the molecule always retains a certain dissymmetry. Better still, he must try to 'tie' the molecule, to put it in a net so that the orientation of the reactive centre is strictly fixed. Nature does this in biological systems where a highly stereospecific interaction between an enzyme (the catalyst) and the substrate takes place; and it is this which the chemist is also learning to do a little at a time, as he slowly uncovers the secrets of catalysis.

Kinetic control and thermodynamic control

Let us now try to analyze a substitution reaction in a molecule containing two asymmetric carbon atoms. Here also we may have kinetic behaviour of the S_N1 or S_N2 type but if we go on to examine the stereochemical aspect we may well be surprised. In particular, by carrying out a reaction in conditions typical for S_N1 reactions we can observe that racemization is not complete, but that the product displays retention or inversion of configuration to a varying degree. If we repeat the reaction on another diastereoisomer of the initial compound the opposite behaviour will most probably be observed: if first there was inversion, there will now be retention and *vice versa*. In other words, starting from either DD′ or DL′ we arrive at a single product (for example, DD′) or at a mixture of products in which one of the two, say DD″, predominates. An analogous reaction, carried out instead in conditions appropriate to S_N2 substitution, shows this effect to a much smaller extent; it is generally possible, by starting two diastereoisomers DD′ and DL′, to reach the two products DD″ and DL″ in a selective manner (Fig. 71).

At this point the thermodynamic properties of the reaction products become very important. In principle the two compounds DD″ and DL″ do not have the same energy. (They are neither identical nor optical antipodes.) The fact that only one of the two is always formed, or alternatively, that the same mixture is formed both by starting from one diastereoisomer (DD′) or from the other (DL′), tells us that the reaction proceeds under thermodynamic control, i.e., tends to give the more stable isomer (or a mixture of two isomers if the difference in free energy between the two is small). On the other hand, if a reaction is controlled kinetically, the two starting diastereoisomers will give two different products, independently of the relative energy levels of these two products. It is obvious that in this case only can we really speak of the stereospecificity of a reaction since, for thermodynamically controlled reactions, the pathway through which the reaction takes place does not have any effect on the products.

Thermodynamic control can be obtained, for example, by the use of very active catalysts or by increasing the reaction temperature. These conditions are those already described for obtaining high reaction rates or, in other words, ensuring that the molecules can easily surmount the energy barrier of activation. The two (or more) reaction products can therefore interconvert in such a way as to reach an equilibrium which may be more or less shifted in favour of one of the isomers. On the other hand, kinetic control is more easily realized with highly selective catalysts, that is to say those which lower the energy barrier for only one and not all of the possible paths of the reaction. Low temperatures will facilitate the selective processes, since the molecule, having little energy, is directed onto one predetermined course. Kinetic control, therefore, allows us to obtain product ratios which are at least partly at variance with thermodynamical predictions, according to which the maximum

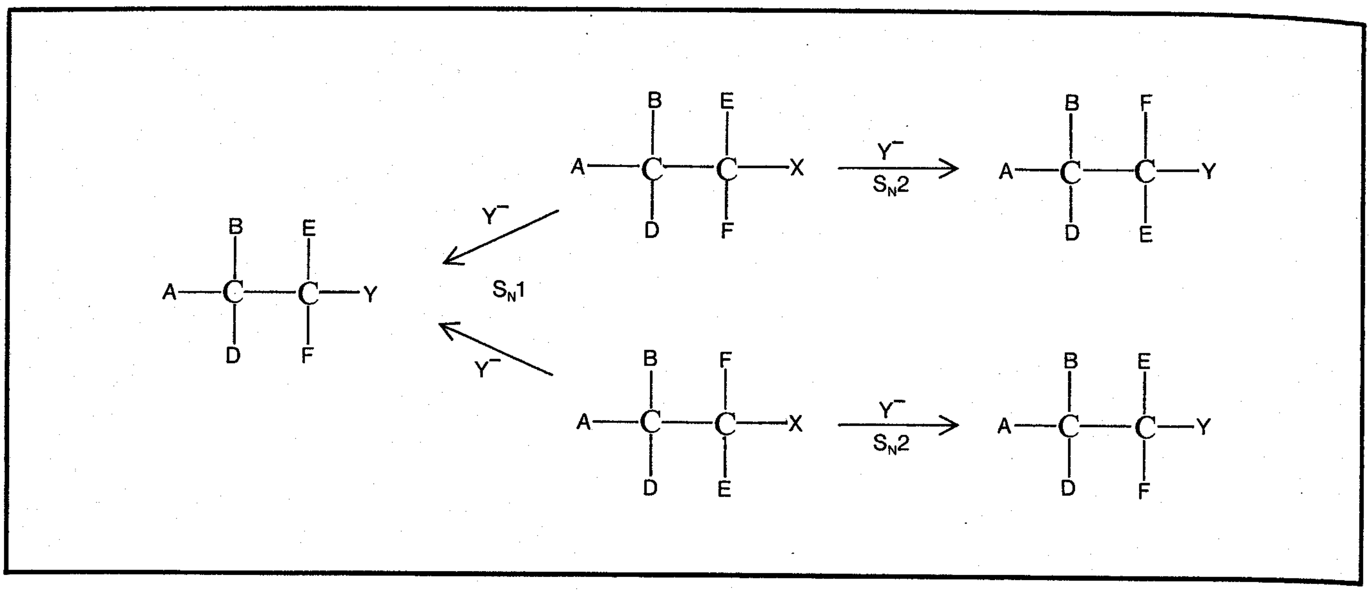


Fig. 71 A substitution reaction of the S_N1 type carried out on two diastereoisomers of a compound containing two asymmetric carbon atoms leads to a single product, the thermodynamically most stable one (or to a mixture always having the same composition). On the other hand, if the reaction takes place through an S_N2 mechanism, two different products are obtained. In the latter case there is kinetic control of the reaction.

lowering of the energy of chemical and physical systems should occur during the reaction.

It is immediately clear that the route preferred by nature in biological processes is the kinetically controlled one. Consider the low temperature (around 37°C) at which chemical processes occur in the human body, the multiplicity of products necessary for life, and the very high selectivity of biochemical reactions.

Partially thermodynamically-controlled reactions are still of very great use in chemical syntheses because they allow us to modify pathways which lead to undesired products. The Diels-Alder

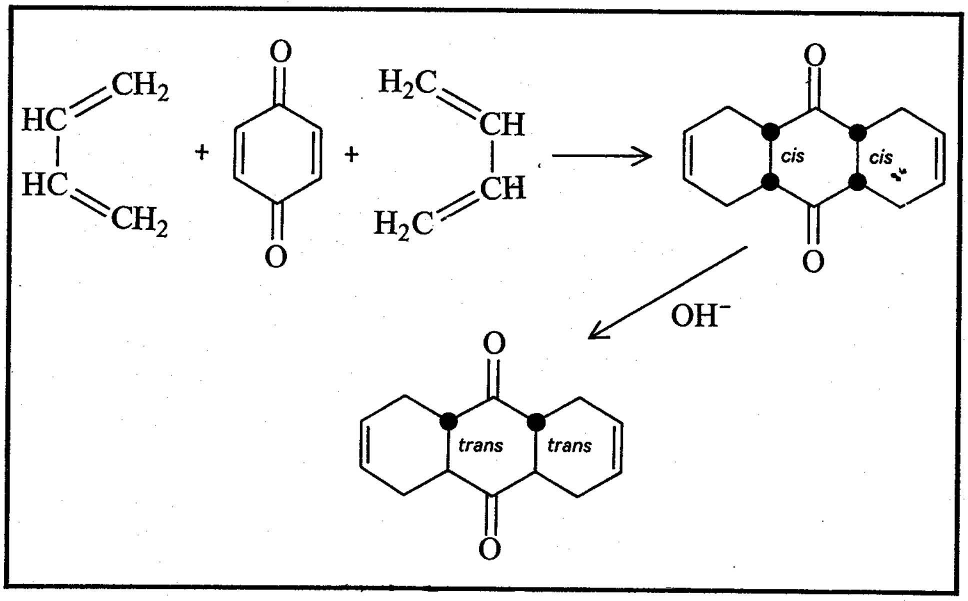


Fig. 72 The Diels-Alder reaction between butadiene and benzoquinone takes place by a *cis* mechanism. The resulting ketone can be isomerized to the more stable *trans-trans* isomer by treatment with alkali.

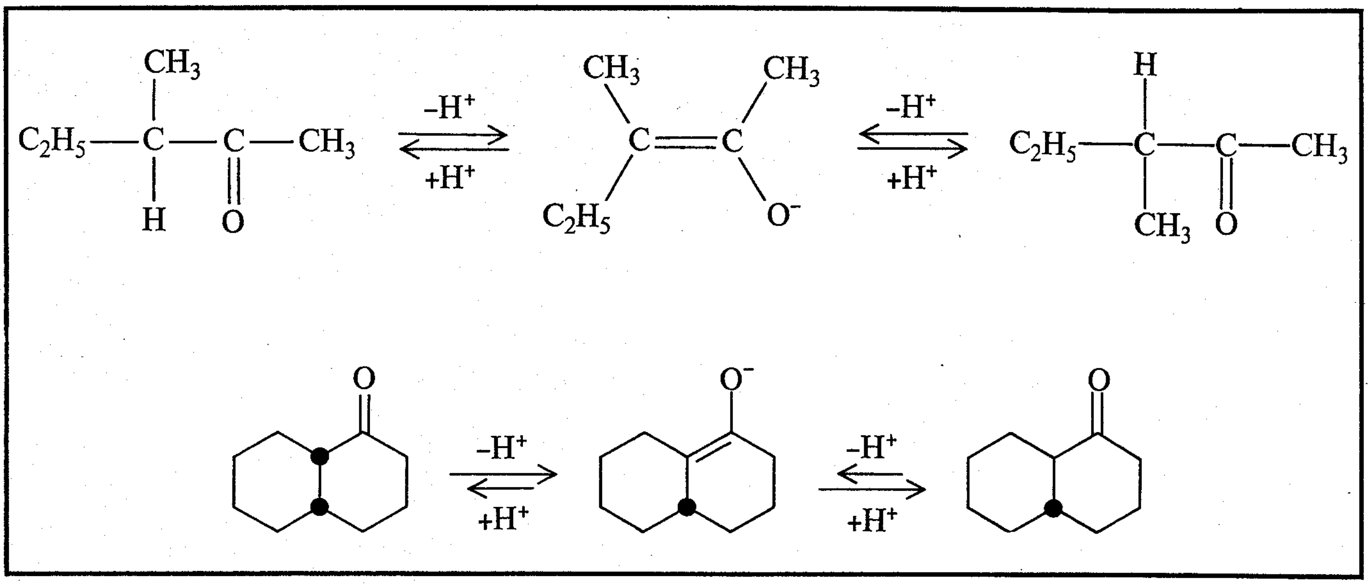


Fig. 73 Optically active *sec*-butylmethylketone rapidly racemizes in alkaline conditions. The reaction intermediate indicated in the centre contains a plane of symmetry and is converted with equal probability into the D and the L compound. However, a ketone with two asymmetric carbon atoms, such as *cis*-α-decalone, is transformed into the more stable *trans* isomer but does not racemize. One of the asymmetric atoms is not touched in this reaction. In contrast to the preceding case, the reaction intermediate is chiral.

reaction, for example, a reaction of the greatest use in the formation of polycyclic systems, has a highly stereospecific mechanism and produces a *cis* junction between two rings (Fig. 72). When, however, a derivative with a junction of the *trans* type is wanted, it is sometimes possible to isomerize the reaction product with a fairly mild treatment. The reaction occurs in two steps; firstly the removal of a proton (H^+) from the ketone, leading to the formation of an unsaturated, negatively charged, planar intermediate (the anion of the enolic form of the ketone) followed by the addition of a proton to regenerate the ketone. But there is a difference compared with ketones containing a single asymmetric atom, such as *sec*-butylmethylketone (3-methylpentan-2-one) (Fig. 73) which has a planosymmetric transition state and thus has an equal capacity for reaction on the two faces. A ketone with two asymmetric carbon atoms, like α-decalone, remains dissymmetric in the transition state. The reactive part of the molecule – the unsaturated carbon atom common to the two rings – is still planar but the plane on which the atoms are situated is not a plane of symmetry. The additions of a proton from one side of this plane or the other are thus not energetically equivalent. The two possible products are not identical and their equilibrium is pushed towards the more stable one, which in this particular case is the *trans* isomer. Starting from the optically active *cis* ketone, it can be seen that the thermodynamic equilibrium has changed the structure but not the optical purity of the compound; the second asymmetric carbon atom is not, in fact, involved in the reaction. The result is totally opposite to that obtained with *sec*-butylmethylketone where the same treatment produces complete racemization of the product.

Asymmetric syntheses

The different behaviour of α-decalone and *sec*-butylmethylketone with respect to the same reagent can be explained by the different symmetry of the respective states. This observation is of general value. The criteria of symmetry which we applied to the study of the stable structure of molecules can be usefully extended to transition states and reaction paths.

The transformation from one dissymmetric compound to another equally dissymmetric occurs without racemization only in the case in which all the intermediate states of the reaction are dissymmetric. Otherwise, a mixture is obtained of laevo and dextro molecules in equal number. This is a consequence of Curie's principle: a physical event cannot have a symmetry lower than that of the event which caused it.* A planosymmetric transition state can therefore yield only non-dissymmetric molecules or a racemic mixture of dissymmetric molecules.

The isomerization from *cis* to *trans*-decalone represents a case of *epimerization,* i.e., partial stereochemical isomerization, in which there is transmission of asymmetry from an asymmetric carbon atom to a reactive point of the molecule. If we start from the optically active compound, for example, (+)-*cis*-decalone, we obtain optically active *trans*-decalone. This process is not, strictly speaking, an *asymmetric synthesis* since this requires, according to the generally accepted definition, the creation of new dissymmetric molecules (in conditions such that the quantity of molecules with the D configuration is different from that of those with the L). But if we only consider the second half of the reaction and, more precisely, the passage of the anion of the enol to the ketone, the definition seems applicable, since the starting compound contains a single asymmetric atom and the final one contains two (Fig. 73). The difference

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* From the *Journal de Physique* of 1894. The original enunciation of Curie's principle is worth quoting:

'Lorsque certaines causes produisent certains effets, les éléments de symétrie des causes doivent se retrouver dans les effets produits.

'Lorsque certains effets révèlent une certaine dissymétrie, cette dissymétrie doit se retrouver dans les causes qui leur ont donné naissance.

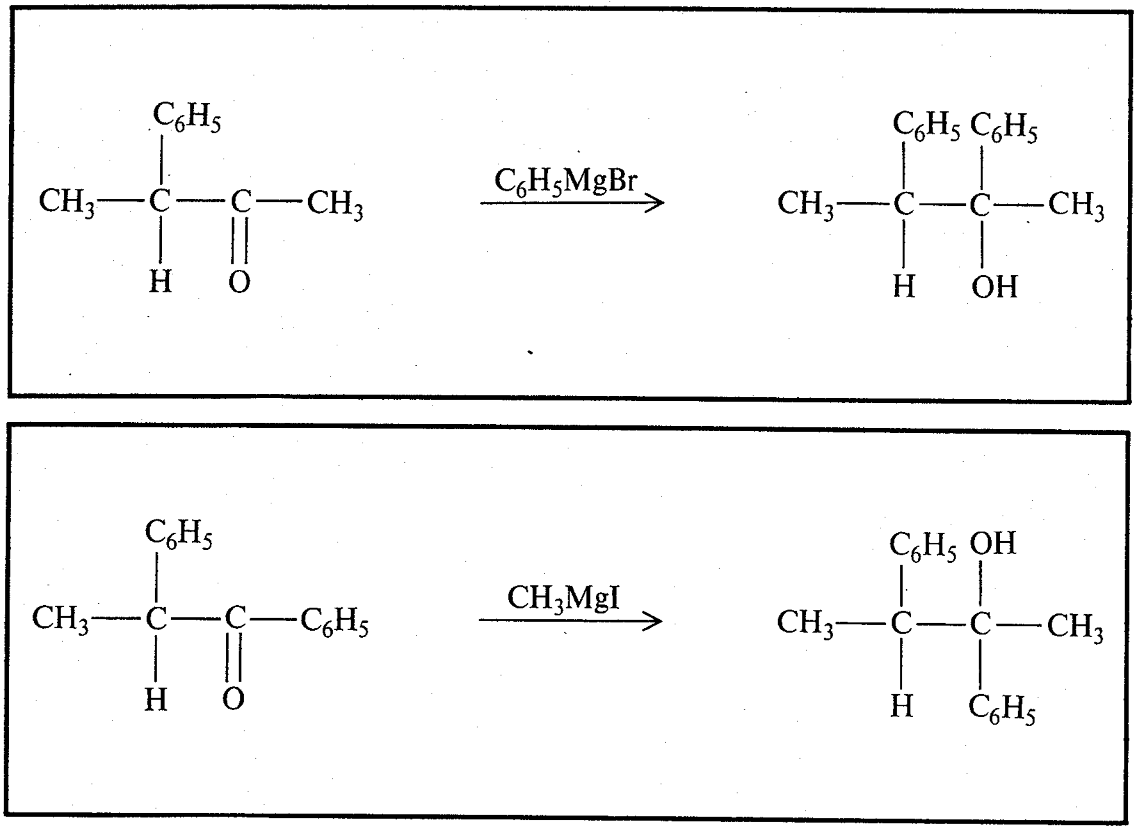
'La réciproque de ces deux propositions n'est pas vraie, au moins pratiquement, c'est-a-dire que les effets produits peuvent être plus symétriques que les causes.'

Apart from the importance which they have had in the development of modern science, these few lines are stylistically exemplary in their conciseness and elegance.

between epimerization and asymmetric synthesis is very small in this case and resides perhaps more in the particular point of view of the observer than in a substantially different physical reality.

In the case just examined the asymmetric induction is caused by thermodynamic factors (the greater stability of the *trans* isomer with respect to the *cis*); elsewhere it may be of a kinetic type, as in the example studied by D. J. Cram (Fig. 74). A dissymmetric ketone, such as 3-phenylbutan-2-one, can be converted into a tertiary alcohol containing two asymmetric atoms by using an organometallic reagent, phenylmagnesium bromide. If one starts from a single optical antipode (for example the D), two different diastereoisomers (DD′ and DL′) should be obtainable; but when the reaction is carried out, one (which we shall call DD′) predominates. An analogous reaction between 2-phenylpropiophenone and methylmagnesium iodide gives the same compounds, but with an excess of the DL′ compound over the DD′. The difference between the two reactions consists essentially in a reversal of the order of introduction of the phenyl and methyl groups. This leads to a very different result at the stereochemical level (the relative abundance of DD′ or DL′). Asymmetric induction is thus kinetically controlled. The isomer which is formed in larger quantity in each reaction is not in fact the more stable but that which requires the overcoming of the lower energy barrier.

Another typical example of an asymmetric synthesis is provided by the reduction of pyruvic acid to optically active lactic acid. Reactions of this type are the oldest known asymmetric syntheses, being studied at the beginning of the century by Marckwald and by McKenzie (Fig. 75). While conceptually no different from the example just given, these reactions present certain aspects on which it is worth dwelling a moment for they help to make clear the normal behaviour of many biological syntheses. By Curie's principle, the transition from pyruvic acid (optically inactive because each molecule is planosymmetric) to optically active lactic acid cannot take place directly. The procedure conceived by Marckwald consists of the transformation of the first compound into one of its esters with an optically active alcohol ((−)-menthol), followed by reduction of this ester to a mixture of diastereoisomers, the (+)-lactate of (−)-menthol and (−)-lactate of (−)-menthol (DL′ and LL′) in unequal quantities. The hydrolysis of the two esters to alcohol and acid then allows optically active lactic acid to be obtained because one optical antipode is more abundant than the other. Other possible methods (even if they are not always technically achievable) for reaching a similar result involve the use of an optically active solvent or of an asymmetric catalyst. It will be remembered that quartz has a dissymmetric structure and causes rotation of the plane of polarized light. If a crystal of optically active quartz is pulverized and mixed with a salt of nickel, a metal-quartz catalyst is obtained which is capable, in particularly favourable conditions, of inducing partial asymmetric synthesis. Other asymmetric syntheses can be carried out on saturaed compounds rather than on the unsaturated types we have examined so far. Glycerol (glycerine), a constituent of animal and vegetable fats, contains three alcoholic groups, two primary and one



$$CH_3-\underset{H}{\overset{C_6H_5}{C}}-\underset{\substack{\|\\ O}}{C}-CH_3 \xrightarrow{C_6H_5MgBr} CH_3-\underset{H}{\overset{C_6H_5}{C}}-\underset{OH}{\overset{C_6H_5}{C}}-CH_3$$

$$CH_3-\underset{H}{\overset{C_6H_5}{C}}-\underset{\substack{\|\\ O}}{C}-C_6H_5 \xrightarrow{CH_3MgI} CH_3-\underset{H}{\overset{C_6H_5}{C}}-\underset{C_6H_5}{\overset{OH}{C}}-CH_3$$

Fig. 74 The reaction of a ketone with a Grignard reagent leads to the formation of a tertiary alcohol. The latter contains the organic residue originally bonded to the magnesium. Inverting the order of introduction of the different organic groups leads to two different stereoisomers. The asymmetry of the ketone exercises an asymmetric induction on the reaction, favouring the formation of particular stereoisomers.

secondary; its molecular structure has an idealized symmetry of the C_s type (i.e., contains only a plane of symmetry). In the majority of its reactions the two primary hydroxyls behave in an identical manner; but when glycerine is made to react with the co-enzyme ATP in the presence of an enzyme it is always converted exclusively into the negative phosphoric ester (Fig. 76).

Glycerol is optically inactive and possesses no asymmetric carbon atom; its central atom is of the C_{ABDD} type (i.e., bonded to two chemically identical substituents). In the phosphoric ester the same atom is bonded to four different substituents (C_{ABDE}), i.e., it is transformed into an asymmetric carbon atom. This is the reason for the optical activity. But why is only one optical antipode obtained? Why

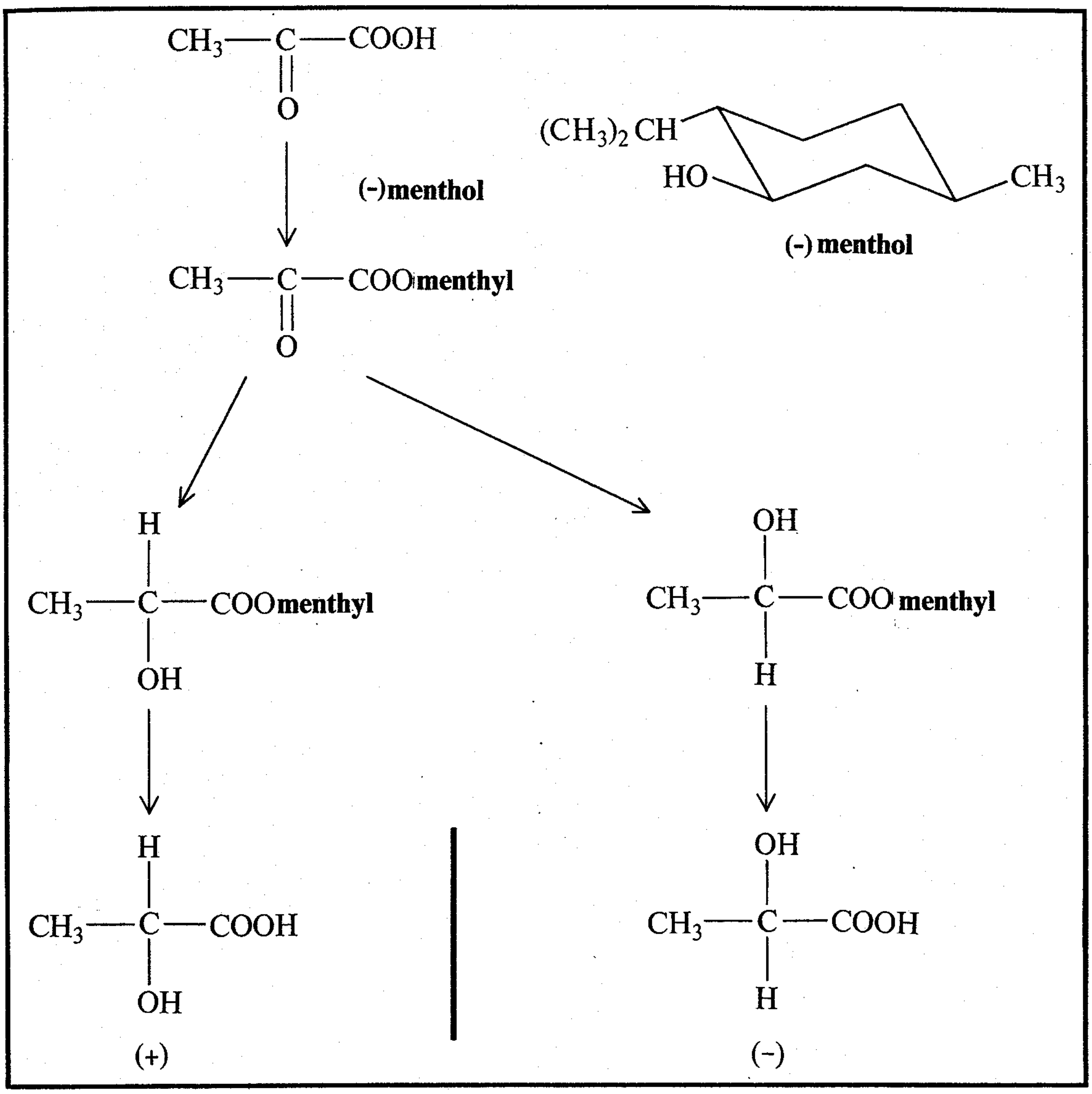
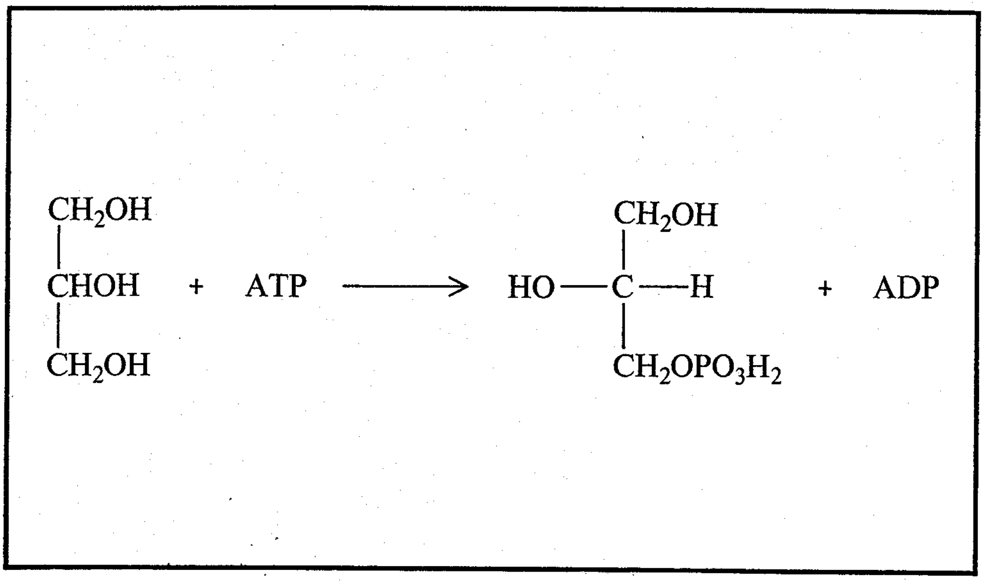


Fig. 75 In the preceding figure we saw an example of intramolecular asymmetric induction. In the asymmetric reduction of pyruvic acid we have a typical example of the intervention of an external asymmetric agent. The reaction between the acid and (−)menthol, an asymmetric alcohol, produces an optically active ester whose reduction gives rise to an unequal quantity of two diastereoisomeric esters. Hydrolysis of the two esters leads to optically active lactic acid owing to the presence of different quantities of the two optical antipodes.

are the two primary hydroxyls no longer equivalent and why does only one of them react?

In order to rationalize this apparently rather strange behaviour, it is useful to introduce the concept of potential asymmetry or *prochirality*. We have said that in the glycerine molecule the only symmetry element is the symmetry plane which divides the molecule into two parts, one a mirror image of the other (Fig. 77). It is possible to see that the two halves of the molecule cannot be superimposed on each other. They behave as two enantiomorphs, or as left and right hands. The two primary alcoholic groups are not, therefore, absolutely identical but are optical antipodes of each other and can be indicated with the letters D and L. The interaction



$$\begin{array}{l}CH_2OH\\ |\\ CHOH\\ |\\ CH_2OH\end{array} + ATP \longrightarrow HO-\begin{array}{c}CH_2OH\\ |\\ C\\ |\\ CH_2OPO_3H_2\end{array}-H + ADP$$

Fig. 76 The phosphorylation of glycerol using the co-enzyme ATP is an example of enzymatic asymmetric synthesis. While the principles are still those of ordinary synthetic chemistry, enzymatic reactions are distinguished by a very high steric selectivity.

of these two groups with a non-dissymmetric reagent (and in surroundings which are also non-dissymmetric) will be exactly equivalent but this is not so for their interaction with a dissymmetric agent, such as the co-enzyme ATP, because here a diastereoisomerism (DD′ and LD′) is created, like those already observed by Pasteur and for which we have already used the analogy of a hand and glove.

This potential asymmetry of glycerol is called prochirality. Other examples of prochiral compounds are shown in Fig. 77; their common characteristic is the absence of rotation axes that link the reactive points of the molecule (the presence of such axes would render such reactive points perfectly equivalent) and the presence of planes or a centre of symmetry. Prochirality is not limited to compounds which contain tetrahedral atoms but can also be observed in many planar species such as olefines, ketones or carbenium ions. The plane of symmetry here also divides the molecule into two enantiomorphous parts which are often called left- and right-handed faces; the addition of a reagent on one or other of the faces leads to two different optical antipodes.

As we have repeatedly emphasized, asymmetric syntheses represent a particular case of the reactions of diastereoisomers. The production of optically active compounds is not magic but only the application of certain methods completely consistent with the principles of symmetry. The process always consists of the employment of some dissymmetric factor (i.e., an optically active reagent) followed by a reaction conditioned by the phenomenon of diastereoisomerism and (usually but not necessarily) ending with a final stage of elimination of the optically active auxiliary agent.

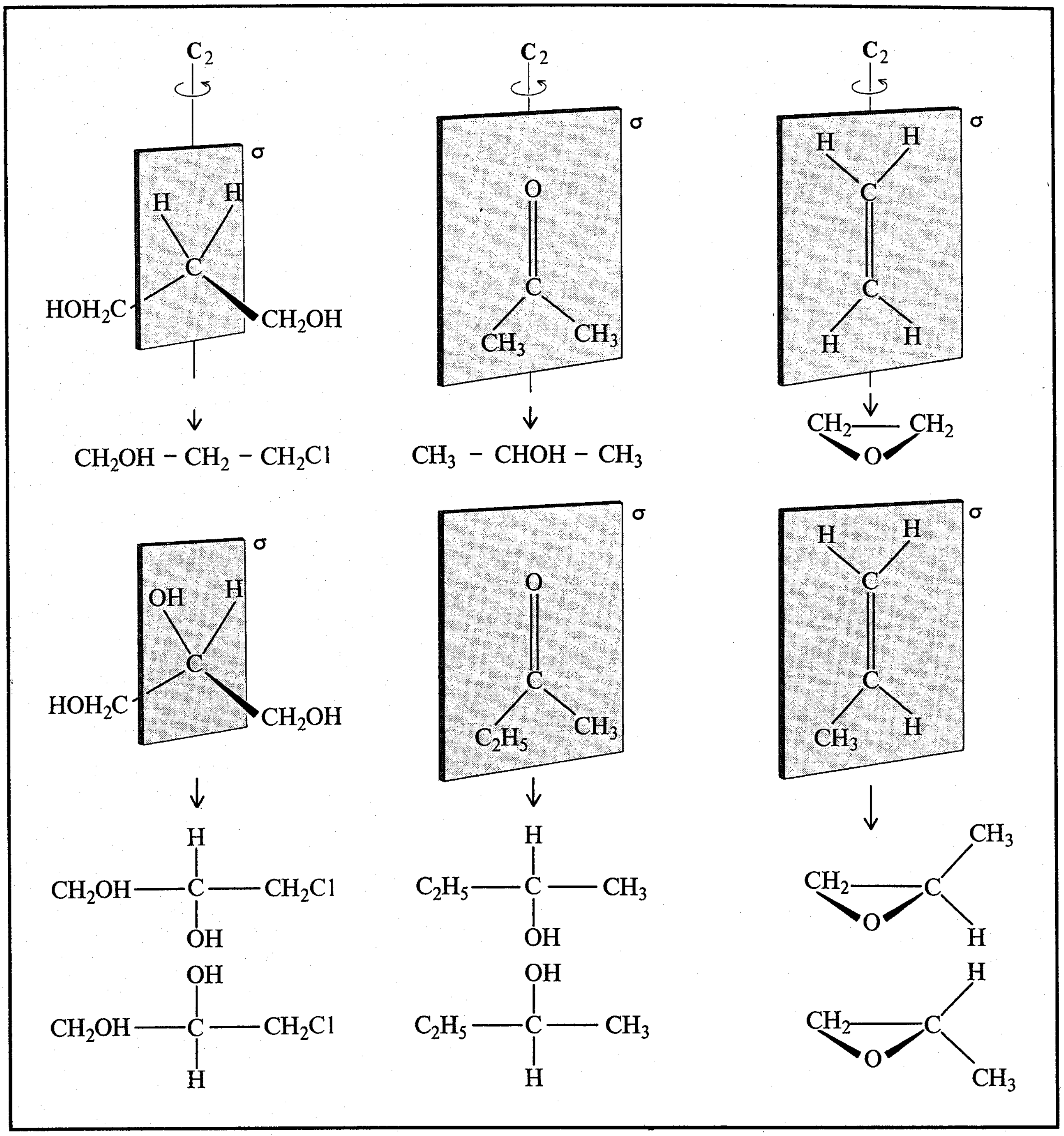


Fig. 77 Examples of prochiral and non-prochiral molecules. The latter are characterized by the presence of rotation axes that connect the reactive points of the molecule and render them perfectly equivalent. Such reactive points can be atoms or groups of atoms or the two opposite faces of a double bond. At the top are some molecules which contain a binary axis and a plane of symmetry; from the left, 1,3-propanediol, acetone and ethylene. They transform, for example, into 3-chloropropanol, *iso*propyl alcohol and ethylene oxide, compounds that do not show stereoisomerism. Below, three examples of prochiral molecules in which the mirror plane is present but not the binary axis. From the left, 1,2,3-propanetriol (glycerol), methylethylketone and propylene. With reactions analogous to those indicated above, they can be converted into 3-chloropropane-1,2-diol, *secondary* butyl alcohol and propylene oxide. These three compounds are asymmetric and exist in enantiomeric forms. With normal synthetic methods the two optical antipodes are obtained in equal quantity; but if an asymmetric factor is present in the reaction, one of the two optical antipodes can be obtained in greater abundance.

It cannot be denied, however, that certain fascinating problems connected with asymmetric synthesis, in particular the origin of optical activity on this planet, still remain unsolved. We shall discuss these problems at the conclusion of this book.

The conservation of orbital symmetry

The summary in the preceding chapter of the relationships between the rules of symmetry and chemical reactivity can now be enlarged upon. The influence of symmetry is not even limited to the large field of stereoselective reactions and of optically active compounds; it is at the base of the very principles of chemical reactions. A great deal of research on this subject has been carried out in recent years since Robert B. Woodward (Nobel prize for chemistry in 1965) and Roald Hoffmann specified the fundamentals of the approach.

The best known and most widely studied examples of reactions controlled by orbital symmetry are the cyclization reactions and those of cycloaddition to unsaturated organic compounds. Butadiene and cyclobutene, for example, are two molecular isomers of formula C_4H_6 which in certain conditions can interconvert. By irradiation with ultraviolet light the first is transformed into the second while the inverse reaction usually occurs by heating to moderately high temperatures. In some cases a thermal cyclization of particular substituted butadienes is also possible. But the most interesting experimental observations are the following. The steric relationships between the reagent and product are always the same in all the thermal processes and are opposite to those observed in the photochemical processes.

Examination of the formulae clearly shows that in the transition from butadiene to cyclobutene the terminal carbon atoms both undergo a rotation of 90°. The substituents, which in butadiene are in the plane of the molecule, move above and below the plane of the ring in cyclobutene (Fig. 78). However, during the conversion, the rotation of the two atoms can occur in the same sense (conrotatory) or in the opposite sense (disrotatory). The experimental data show that all the thermal processes which convert a butadiene into a cyclobutene, and vice versa, take place in a conrotatory way and all the photochemical processes in a disrotatory way.

Analogous behavior is observed in the interconversion between hexatriene and cyclohexadiene (Fig. 78), but here the mechanism is exactly reversed. The photochemical reactions take place in a conrotatory way and the thermal ones in a disrotatory way.

To illustrate, even in an elementary way, the interpretation proposed by Woodward and Hoffman it is necessary to introduce some

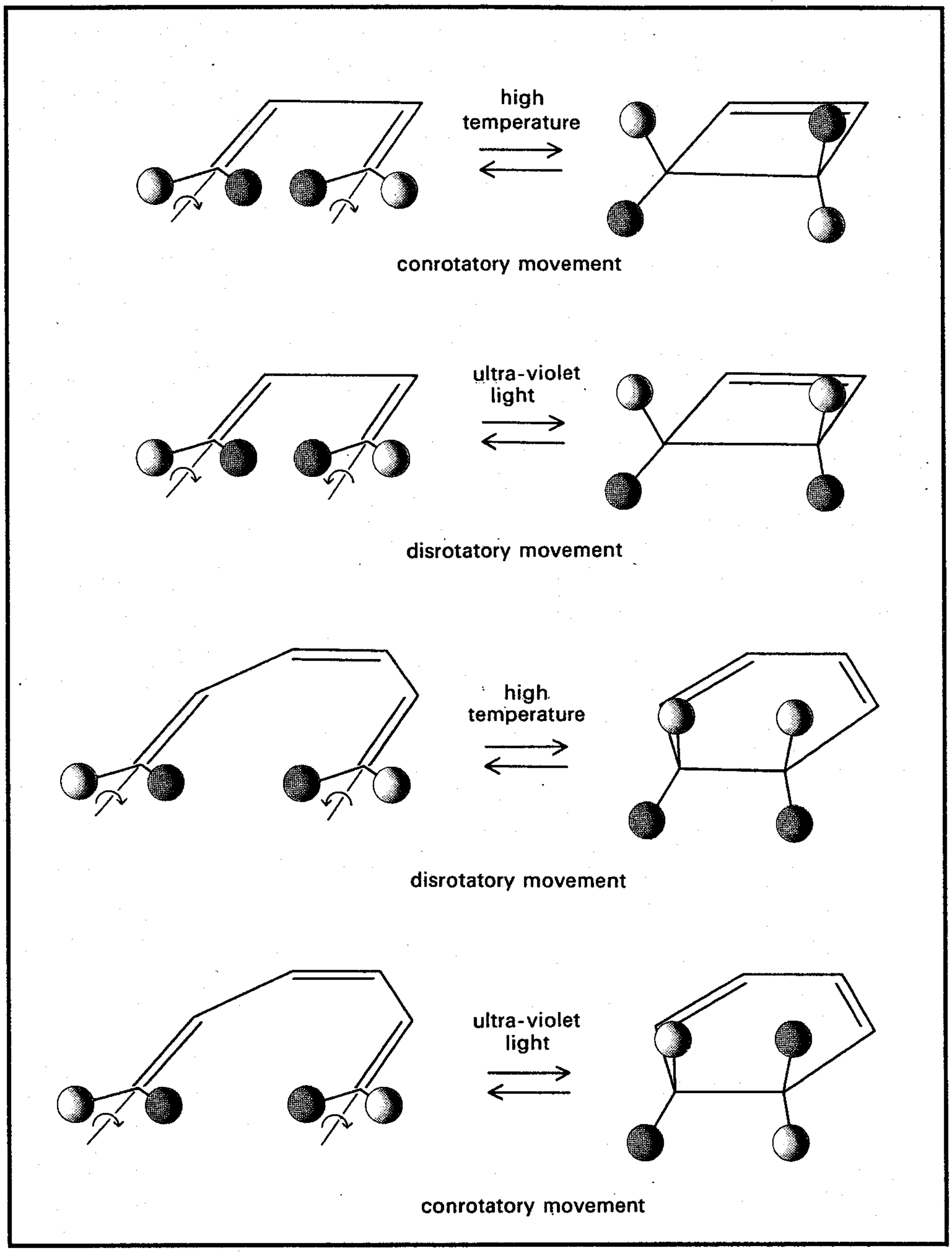


Fig. 78 **The interconversion between butadiene and cyclobutene occurs, depending on the experimental conditions, through different stereochemical pathways, which can be distinguished by introducing suitable substituents into the molecule (indicated here with a different shade of colour). The analogous reactions between hexatriene and cyclohexadiene occur with a mechanism opposite to the previous ones.**

elements of the theory of molecular orbitals. In describing the structure of the atom and of molecules we have already indicated the sign, positive or negative, of the lobes of the *p* and *d* atomic orbitals and the fact that the molecular orbitals are obtained by superimposing and summing a suitable series of atomic orbitals. In technical terms this process is called the linear combination of atomic orbitals; hence the abbreviation LCAO to indicate the simplest version of the theory of molecular orbitals. In the discussion on the structure of the ethylene molecule (see page 56 and Fig. 23), we have seen the existence of σ and π bonds; we must now state that, as for the σ bonds, the theory predicts the existence of a second orbital for the π bonds, called antibonding or π^*, which does not normally contain electrons and has an energy level higher than that of the π orbitals.

For unsaturated compounds which contain two or more double bonds separated by a single bond (the so-called conjugated dienes or polyenes) the number of orbitals of the π or π^* type is equal to the number of unsaturated carbon atoms present in the molecule. For example, in butadiene, $CH_2{=}CH{-}CH{=}CH_2$, there are four orbitals of this type and they are obtained by combining with different signs the four *p* orbitals of the carbon atoms (Fig. 79). Their energy depends on the number of nodes (inversions of sign) in each molecular orbital. The most stable has no node (that is to say the orbitals all have positive signs), while the least stable has three (all of the adjacent atomic orbitals have opposite signs). The four electrons available for the π orbitals – their number is determined by a reasoning analogous to that developed for ethylene – will be found therefore in two pairs in the two orbitals of lowest energy.

Our attention must now be centered on the two middle orbitals (also called frontier-orbitals), i.e., the highest occupied and the lowest unoccupied orbital. The Woodward-Hoffmann rules state that the reactions just examined are governed by the symmetry of the highest occupied molecular orbital. For the 'thermal' processes such an orbital is the second lowest, and is occupied by two electrons, while for the photochemical reactions an electron is displaced from the ground state to an excited state with higher energy. The highest occupied molecular orbital now corresponds to the lowest energy vacant orbital in the ground state.

It is possible to give an analogy for the choice of these orbitals by remembering what we said concerning atoms. The chemical behaviour of the various elements depends in large measure on their position in the periodic system or, in other words, on their external electronic configuration. The external electrons are the most mobile and are thus those exchanged most easily between the atoms in the formation of chemical bonds. In its turn, the molecule can be considered in certain respects as a pseudo-atom and thus it seems reasonable to attribute to the external electrons a marked influence on reactivity.

Let us now look at the occupied orbital with maximum energy in butadiene (Fig. 80); the wave function has opposite signs on the terminal atoms. If a σ bond is to be formed (and remember that to form such bonds it is necessary to superimpose two orbitals with the same sign), there is no other possibility but to rotate the two orbitals in the same sense. The formation of the cyclobutene ring

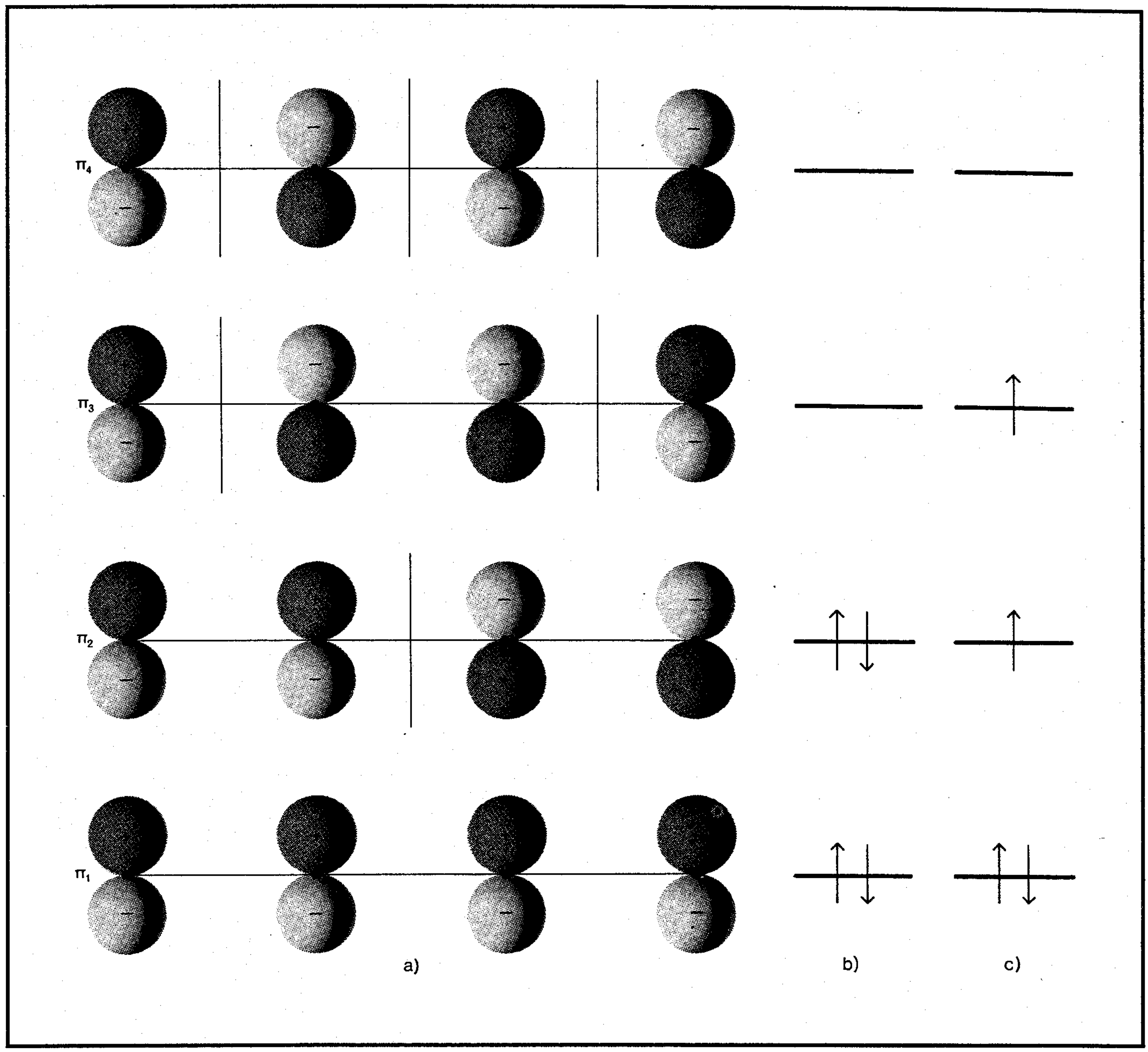


Fig. 79 A scheme of the π molecular orbitals of butadiene. The signs of the wave functions around each atom and the number of nodes are indicated (the thin vertical lines). The energies of the orbitals increase from the bottom. In the centre, the ground electronic state of butadiene with the electrons paired (each arrow indicates an electron). Under the action of ultraviolet light, one of the electrons acquires energy and goes into the higher orbital (right). This is referred to as the excited state.

starting from a butadiene molecule in the ground state thus requires a conrotatory movement which is experimentally observed in the reactions carried out at high temperature.

This reasoning can be repeated for an excited molecule of butadiene. The symmetry of the third orbital of butadiene is different from that of the second, examined above; the signs allotted to the terminal atoms are (+) (+) rather than (+) (−). The formation of the σ bond thus imposes a disrotatory movement in agreement with what is observed in the photochemical cyclization reactions.

The connection between the interpretative hypotheses and experi-

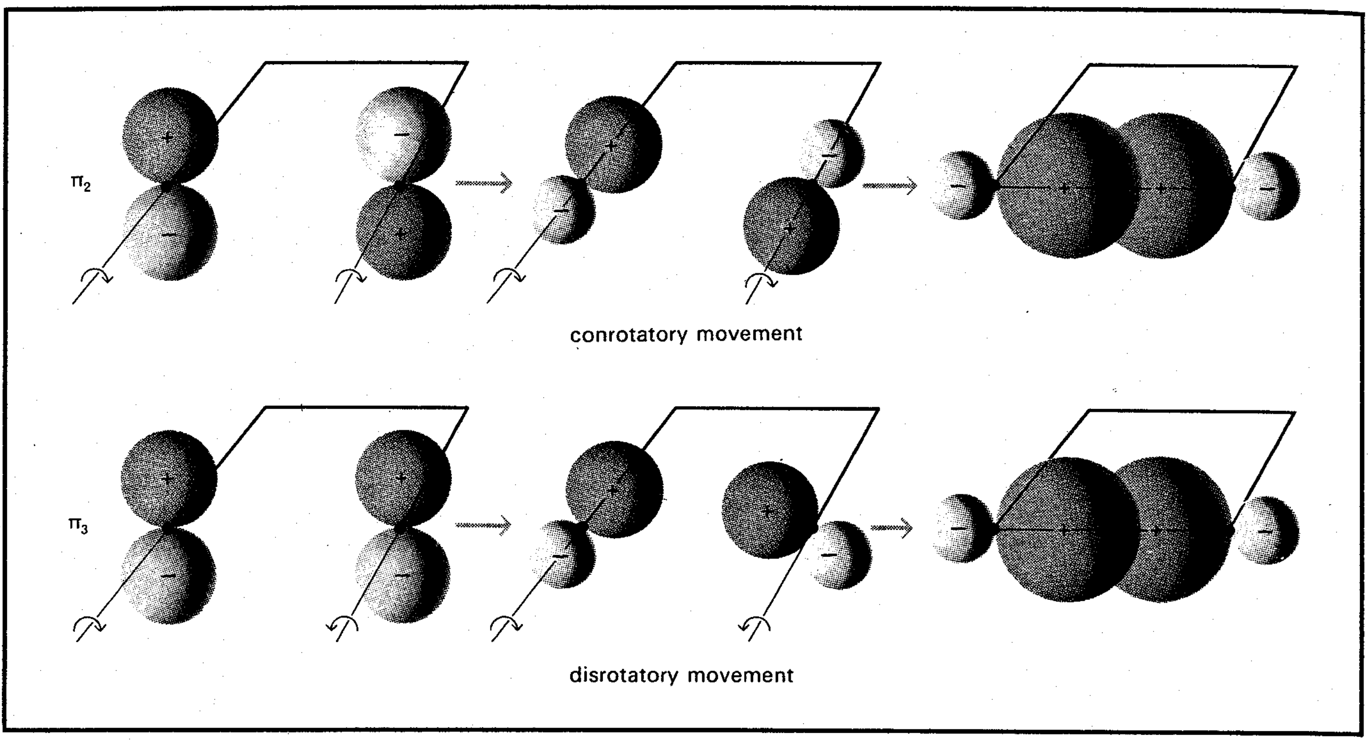


Fig. 80 **Transformation of the π_2 (upper) and π_3 (lower) orbitals of butadiene into the σ orbital of cyclobutene. Because of the different type of symmetry, the process occurs with a conrotatory movement for π_2 and a disrotatory one for π_3.**

ment does not finish here. If the diagram of the molecular orbitals of hexatriene is constructed we see that the symmetry of the two orbitals in question (the highest occupied and the lowest non-occupied) is reversed with respect to butadiene. This is the justification for its chemical behaviour, a behaviour opposite to that of butadiene. This phenomenon is of a general type and it is possible therefore to give a general rule: thermal processes of cyclization occur in a conrotatory way for all the polyenes for which the number of π electrons is a multiple of four (4, 8, 12, . . . etc.), and in a disrotatory way when such a number is even, but not a multiple of four (6, 10, 14, etc.). For photochemical reactions the rule is reversed.

Many other organic reactions have been interpreted in an analogous manner. More recently the same type of reasoning has been extended to the study of simple inorganic and catalytic reactions.

The treatment of Woodward and Hoffman, of which the simplest version was given here, is not quantitative; it is obtained from general considerations of the principles of symmetry and neglects both the approximations which are usually employed in quantum-mechanical calculations and the detailed constitution of the molecule under examination. Obviously, its reply can only be simple: yes or no, where *yes* means that the reaction is symmetry-allowed. But it is still necessary to take account of all the other conditions which limit the reactivity of the molecule. *No* means that the reactivity of the molecule is very low and the predicted reaction, if it occurs, will have to be carried out under drastic conditions or will proceed according to a different mechanism.

VI

Macromolecular stereochemistry

Atoms and molecules are extremely small entities. To appreciate this, it is sufficient to know that their dimensions are measured in nanometers (nm), one of which corresponds to one thousand-millionth of a metre and if it is necessary to express the weight of common molecules like water and oxygen in terms of grams, more than twenty zeros must be written to the right of the decimal point before finding some significant numbers. The sum of the weights of all the atoms contained in a molecule of a given compound is the molecular weight of the compound. The relationship between the units of atomic and molecular weights and the unit of macroscopic mass, the gram, is expressed by Avogadro's number, i.e., $6{\cdot}06 \times 10^{23}$. This means that in 18 grams of water (for which the molecular weight is 18) there are $6{\cdot}06 \times 10^{23}$ molecules of water.

However, even in this extremely small world there are dwarfs and giants. The majority of organic compounds have a molecular weight below 1000. When one speaks of organic chemistry without further qualification, one is usually referring to this range of molecular sizes. Within this limit the properties of compounds certainly depend somewhat upon molecular weight but not really to the point where the differences become qualitative. However, when the molecular weight rises much above 1000, the properties of the material become substantially different; the compound is then called a macromolecule or a polymer and the discipline which specializes in such compounds is called macromolecular, or polymer, chemistry. The significance of this term should be understood in the context just illustrated; these huge molecules are such only with respect to other molecules and not in comparison with the objects daily observed by us. A molecule of a hydrocarbon with a molecular weight of 100000 (such as that used for polythene bags and plastic boxes), extended to its maximum length, always measures less than 1000 nm, or less than a thousandth of a millimetre, and has transverse dimensions of 0·4 or 0·5 nm. In practice it assumes a more folded form and it may be compared to a sphere with a diameter of a few tens of nanometers, very much below the resolving power of any optical microscope.

The frequently used term 'polymer' indicates a further important property of this class of substances. The term, the opposite of 'monomer' reflects the way in which macromolecules can be obtained: by the use of a chemical reaction in which many small molecules are joined together. Such a reaction is termed 'polymerization'.

With the exception of metal objects, most of the matter we touch and use in daily life is made from macromolecules. The modern era has been called the era of plastics. Plastic materials, textile fibres and rubbers are all macromolecular substances. Furthermore, many compounds of natural origin belong to this class: leather, wool, cotton, wood and paper and even the majority of foodstuffs and living matter itself.

Because of the different aims and techniques of investigation, macromolecular chemistry is traditionally divided into two parts, one relating to synthetic macromolecules and the other to natural ones. We shall start with the former and, by introducing fairly elementary ideas, we shall cover the stereochemical aspect in particular. Later we shall illustrate those real marvels of nature, the proteins and nucleic acids.

Synthetic polymers

Macromolecular chemistry has a recent history. The first definitely planned polymerization reactions were carried out in the first years of this century, when Leo Baekeland obtained a synthetic polymer of practical use, bakelite. But it was Hermann Staudinger, who, around 1920, developed the fundamental principles of the science.

The study of polymeric materials is not an easy one and requires the application of techniques and theories not required in normal organic chemistry. We have already said that the molecular weight of a macromolecule is several orders of magnitude greater than that of normal organic compounds; in general it can vary between 10000 and several million units. The determination of this weight may require measurements of the viscosity of solutions or of osmotic pressures; special methods, such as measurement of the diffusion of light or ultracentrifugation, may also be required. But even before these methods could be applied to the search for the relationship between the data thus obtained and the quantities to be measured, there were even more fundamental problems to resolve. The most important of these was the basic problem of the nature of polymers and the reasons for their particular properties.

One of the most interesting and most intensely studied macromolecules is natural rubber, obtained from the latex of *Hevea brasiliensis*. Even in the nineteenth century this had assumed great technical and industrial importance. Its fundamental unit was precisely determined by chemical methods. It was found that rubber was an isoprenic substance, i.e., one formally derived from isoprene, and in this it was analogous to many natural substances also based on this unit (terpenes, steroids, etc.). We know today that rubber is a polymer of isoprene or, more exactly, a *cis* polyisoprene of high purity but, fifty years ago, its structure was still being discussed on an erroneous basis. It was considered to be a combination of cyclic compounds of relatively few carbon atoms (10 or 15 for example) bonded by special forces characteristic of these substances (Fig. 81).

Staudinger took a firm stand against this concept and with a notable series of experiments succeeded in upsetting the accepted view. He proposed a new theory: polymers consist of very big molecules in which the forces between the atoms are the same as those which characterize ordinary chemical compounds of low molecular weight. This hypothesis is now known to be correct.

With the problem of structure solved, chemical industry suddenly understood the importance of this research and undertook a large part of it. Thus several groups of scientists were formed around 1930, among which the most famous were those directed in Germany by Hermann Mark and in America by Wallace Carothers. The discovery and development of numerous materials which are in common use today is due to them: polystyrene, vinylic and acrylic polymers and nylon. But beyond these great industrial successes there was also a development of theoretical knowledge. Rarely has collaboration between science and industry been so close and reciprocal.

One of the first results to emerge from this research was an understanding of the fundamental mechanisms of the polymerization processes. These can be subdivided into polyaddition processes (more properly called polymerization) and polycondensation processes. The first consist of the joining of many, generally unsaturated, small molecules, containing one or more carbon-carbon double bonds, to produce a gigantic molecule in which the various monomeric units are joined together with normal covalent bonds (Fig. 82). Among the innumerable examples, we might mention ethylene, styrene, vinyl chloride, methyl methacrylate and butadiene, which are respectively converted into polyethylene, polystyrene, polyvinyl chloride, polymethyl methacrylate and polybutadiene. In this last case the monomer contains two double bonds and displays a par-

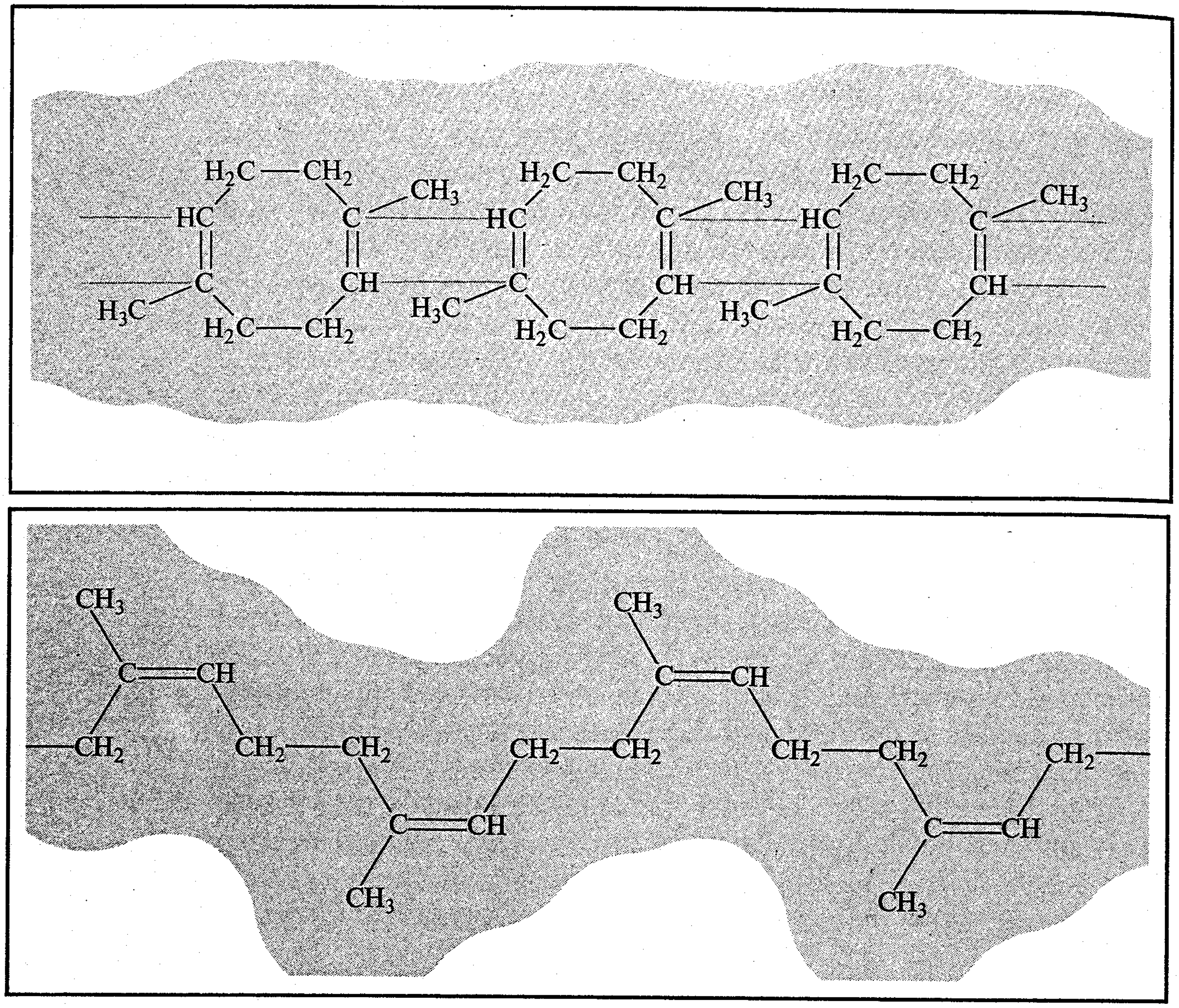


Fig. 81 The structure of natural rubber as it is interpreted today (below) and as it was understood fifty years ago. Before the macromolecular theory was accepted, special intermolecular forces were believed to exist which held together cyclic units of low molecular weight and gave the rubber its characteristic properties.

ticular reactivity: it can react, for example, with only one double bond or with both. Radically different products are obtained in the two cases.

In addition to the polymerization of pure monomers, one can frequently obtain a co-polymerization of two or more monomers. In this way the technological properties of the products may be varied within wide limits. In this connexion, it is interesting to recall that the co-polymer butadiene-styrene, known in Germany as Buna S and in America as GRS, played a major part in the last war. The events of war had made it impossible for all the protagonists (with the exception of the Japanese) to obtain natural rubber from the Far East. The scarcity of rubber was foreseen in time in Germany and Russia and, consequently, the research and production of

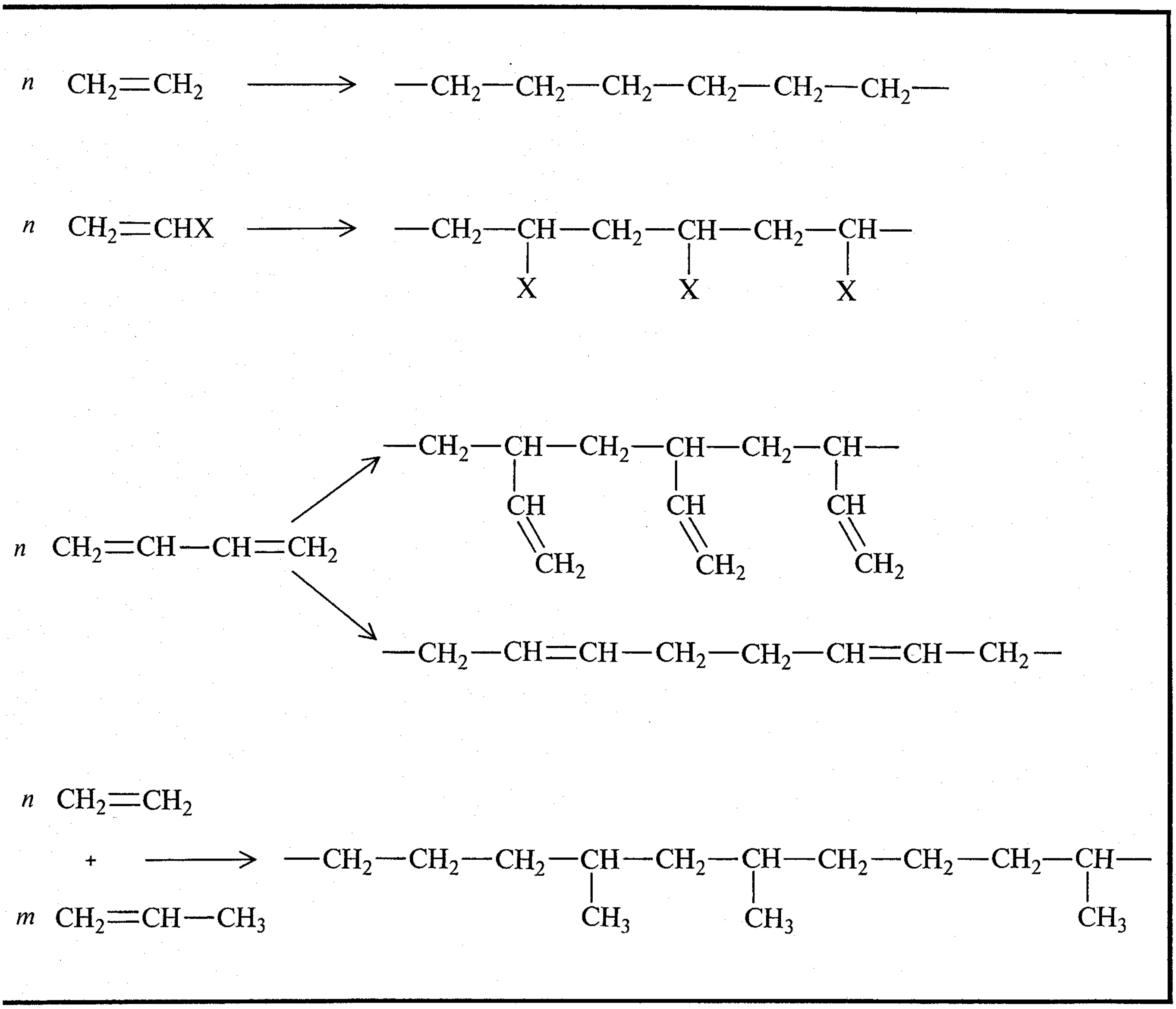


Fig. 82 **Some examples of polymerization or polyaddition, with the formulae of the monomer and the polymer. From above: ethylene and a vinyl derivative. (If X is an atom of chlorine, vinyl chloride is obtained; f X is a methyl group the derivative is propylene; and if X is a phenyl group the derivative is styrene.) Next, butadiene which can polymerize in two ways with a 1,2 or a 1,4 linkage. Finally, an example of copolymerization between ethylene and propylene.**

synthetic rubber was greatly developed by the industry of these countries. On the other hand, the catastrophe of Pearl Harbour and the rapid Japanese expansion in south east Asia caught the American military by surprise. The effort that United States industry undertook to overcome this difficulty was immense. Perhaps not even the Manhattan project for the production of the atomic bomb was so significant for the result of the second world war and hence for the subsequent political situation.

Polycondensation reactions differ in many ways from true polymerizations. The most conspicuous difference arises from the fact that the macromolecule is not made from the sum of all the atoms contained in the monomers. In the condensation there is generally a formation of some very simple by-products (water,

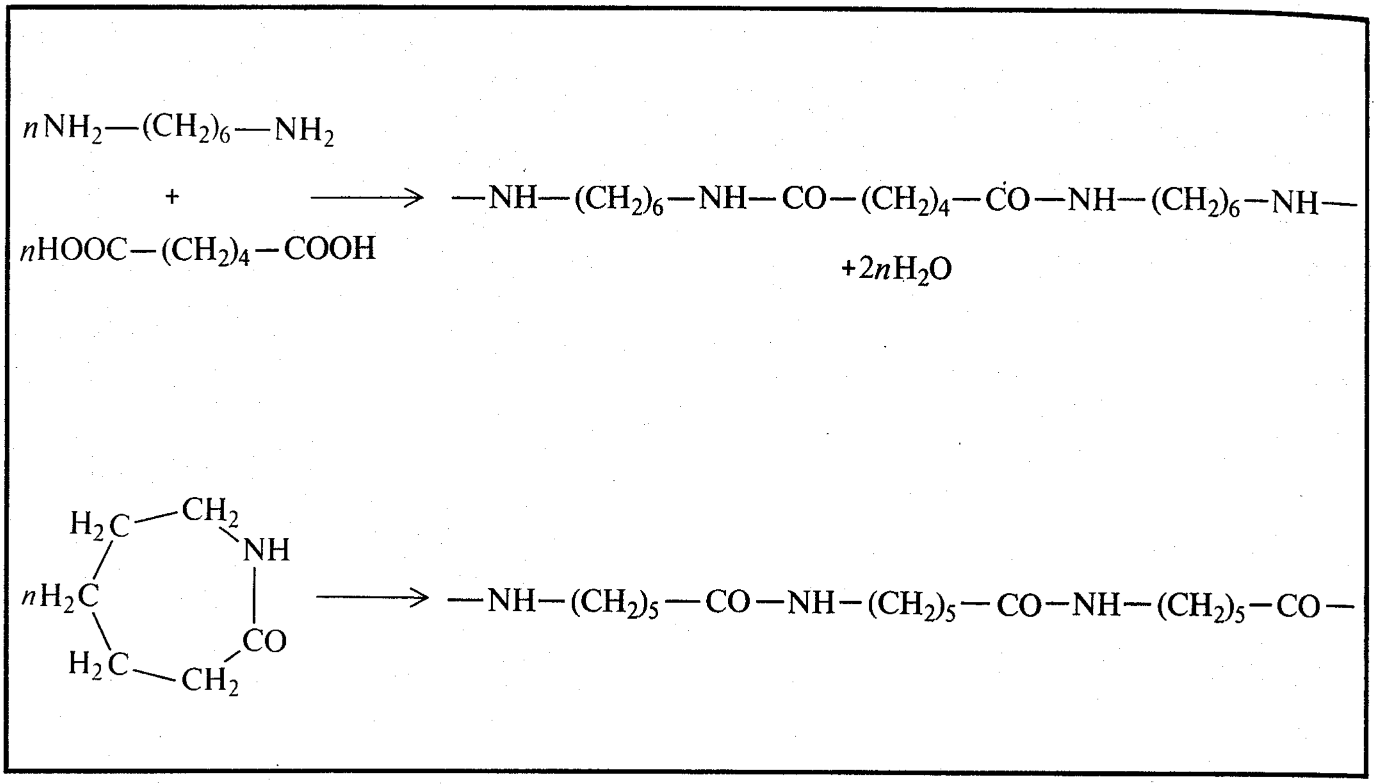


Fig. 83 **The synthesis of Nylon 66, starting from hexamethylenediamine and adipic acid, is a classic example of polycondensation with the elimination of water molecules. The synthesis of Nylon 6 by opening of the ring of caprolactam, a heterocyclic compound, is also considered to belong to this class, even though it occurs without the elimination of any by-product.**

ammonia), in a definite stoichiometrical relationship (one to one or one to two) with respect to the reacting molecules. Moreover, in contrast to the polyadditions in which each monomer is bonded to the growing polymer during a chain reaction, in polycondensations the monomer molecules first react by forming dimers, trimers and other short polymers and subsequently these react with each other to give polymers of higher molecular weight (stepwise reaction). A classical example is the reaction for the formation of Nylon 66 starting from adipic acid and hexamethylenediamine (Fig. 83).

The applicability of the term polycondensation is enlarged below, by including other reactions which do not lead to the elimination of by-products, but in which many characteristics of the reaction are substantially analogous to those of typical polycondensations. In this respect the synthesis of Nylon 6, starting from caprolactam, should be mentioned.

Organometallic catalysts

A polythene molecule ideally consists of a succession of thousands of -CH_2- groups bonded to each other in a manner which makes a long, completely regular, chain. This is rather an approximate description, because the polymerization conditions – high temperatures and pressures of several thousand atmospheres are employed – are so severe that the real process is much more complex. The macromolecules of polythene are not perfectly linear; they have numerous branches which markedly change the properties of the product. For example, polythene obtained under high pressure conditions has a rather low melting temperature (105–115°), a fact which placed a serious limitation on many technical applications.

A substantial improvement in the synthesis of polythene was made in 1953 by Karl Ziegler, the 1963 Nobel prize winner for chemistry, and his research group at the Max Planck Institute at Mühlheim. Ziegler had great experience of the reactions between metals and hydrocarbons and of general organometallic chemistry. His studies on Buna, the first synthetic rubber of any importance, which was obtained by using sodium, an extremely reactive metal, are well known. His later discovery in the field of polymerization was exceptionally important, not only for its industrial value in the process he developed – the synthesis of polythene at low pressure – but for the great versatility and efficiency of the catalysts he discovered. In the Ziegler process, ethylene is polymerized at room temperature and pressure in the presence of certain aluminium and titanium compounds, conditions being such as to ensure the absence of oxygen and moisture. The polythene thus obtained has a more regular structure, melts at around 135°C and closely approaches what we can call an ideal, linear macromolecule (Fig. 84).

The sequel to this story closely concerns Italian chemistry and the very authors of this book, since the new macromolecular chemistry or, better, macromolecular stereochemistry, was born and developed at Milan Polytechnic beginning in 1954.

The Ziegler catalysts were extremely active and transformed a

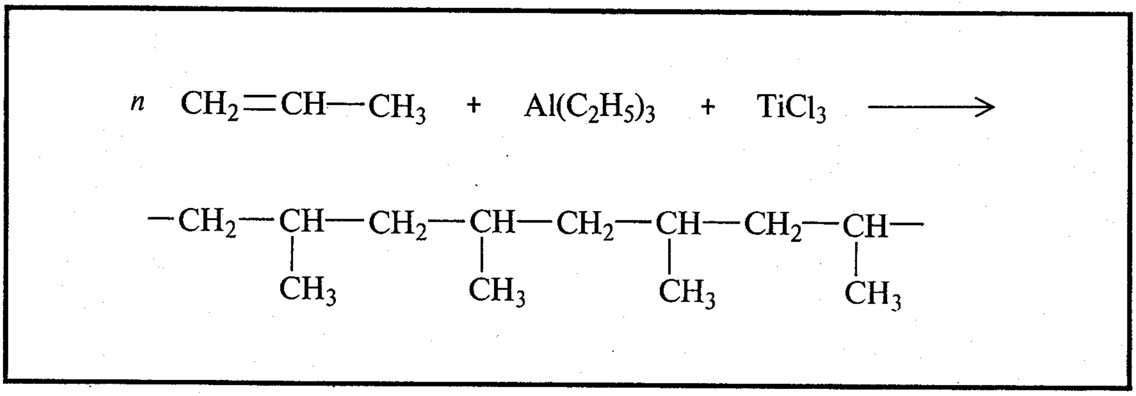
$$n\ \mathrm{CH_2{=\!=}CH_2} + \mathrm{Al(C_2H_5)_3} + \mathrm{TiCl_4} \longrightarrow$$

$$-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{CH_2}-\mathrm{CH_2}-$$

Fig. 84 The low pressure polymerization of ethylene was realized by Ziegler using the product of the reaction between triethylaluminium and titanium tetrachloride as a catalyst. The polymer is very much more regular than that obtained by conventional methods.

difficult and dangerous process, such as the polymerization of ethylene at high pressures, into a reaction which can be carried out in the laboratory with normal glass apparatus. We then asked ourselves what would happen if, instead of ethylene, an attempt was made to polymerize other very much less reactive compounds, such as propylene or butylene, and also other traditional monomers, such as styrene and butadiene. The reply to these questions was a surprise. The former compounds were easily transformed into the corresponding high molecular weight polymers; the latter gave rise to a completely new type of product with totally different characteristics from those of previously known polymers.

At the experimental level, however, matters were not very simple. We still remember the series of completely negative trials that followed some encouraging indications. The techniques were still not very well understood and the necessary experimental subtleties, those well-known tricks of the expert which exist in every field, were not known. It was only after a very careful examination of the results, when the decision was made to change one of the constituents of the catalyst, that the process became substantially better, both in respect of reproducibility of results and quality of product. The first trials on propylene were carried out with the typical Ziegler catalyst, obtained by the reaction of titanium tetrachloride with triethyl aluminium (a very dangerous compound owing to its exceptional reactivity), and consisting of a brown or black liquid-solid mixture. When propylene, a gas quite similar to the normal liquid gas obtained in cylinders, was placed in the presence of the catalyst, it was converted into a blackish, gelatinous mass. After a long purification process a 30–40 per cent yield of a white solid was obtained – crystalline polypropylene. The decisive improvement came with the substitution of titanium tetrachloride by titanium trichloride, a violet-coloured, crystalline powder. With the new



$$n\ CH_2{=}CH{-}CH_3 + Al(C_2H_5)_3 + TiCl_3 \longrightarrow$$

$$-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-$$

Fig. 85 In the presence of similar catalysts (for example, made from triethyl aluminium and titanium trichloride) propylene is converted into a product that has never been obtained by other methods: isotactic polypropylene, melting-point 175 °C.

catalyst, crystalline polypropylene was obtained directly in the form of a white powder and with a yield greater than 90 per cent (Fig. 85).

This polymer melts at about 175°C, is almost insoluble in any common solvent, can be converted into fibre of the highest strength or into thin, transparent sheets or films, or can be converted into fabricated objects of endless shapes and sizes.

Isotactic and syndiotactic polymers

The most interesting aspect, however, was the structure of polypropylene and the other high polymers obtained by this method. The normal means of investigation used by macromolecular chemists were found to be rather inefficient. Instead it was the use of a technique rarely used in this field until that time which allowed the problem to be solved. This technique was the diffraction of X-rays, the typical method for the investigation of crystals.

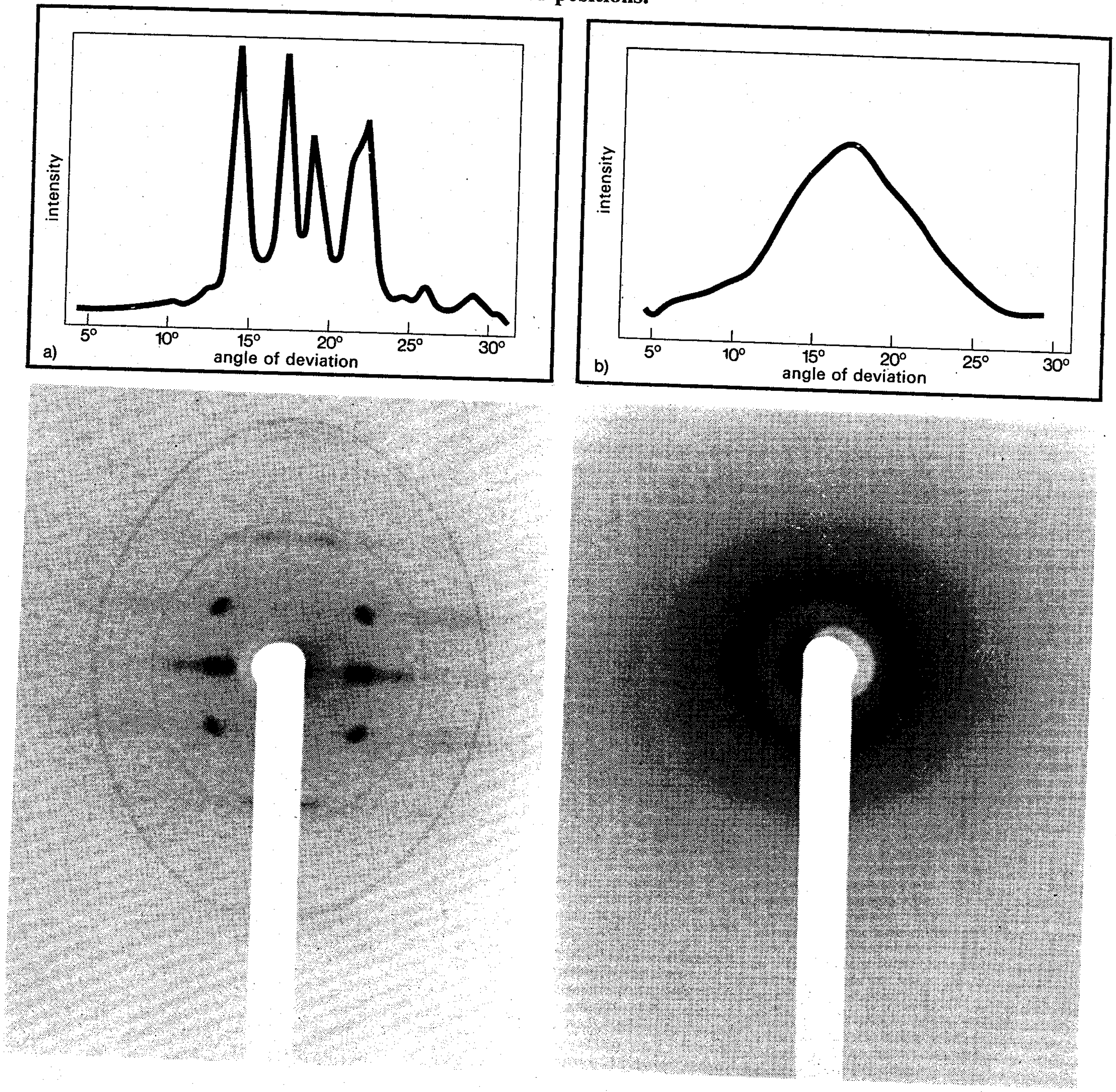
A crude sample of polypropylene examined with an X-ray diffractometer shows a certain crystallinity, even though it does not show any signs of macroscopic crystals. Its crystallinity is notably increased by enrichment operations and by suitable thermal treatment and can be better observed if the polymer is converted, by fusion and extrusion, into a thread and subsequently stretched until it has increased to several times its original length (Fig. 86).

Crystallinity is an indication of the order existing at the molecular level. Crystals are formed from molecules or ions regularly arranged in a three-dimensional way according to very precise rules defined by the different symmetry elements: rotation and translation axes, planes and centres of symmetry and their combinations. For the existence of an ordered crystal, the presence of a single type of molecule is necessary, or of a few well-defined types of molecules or ions (we neglect the case of isomorphism and that of inclusion compounds) whose positions are regularly repeated in space.

A linear polymeric chain has, however, some particular characteristics, for example, the enormous difference between its length and cross-section and the fact that it already possesses within itself repetitions of the successive monomer units. These two characteristics ensure that the crystallinity of polymers is both an intermolecular and an intramolecular phenomenon. This is the typical feature of macromolecular stereochemistry. A three-dimensional order can only be obtained if there already exists a mono-dimensional order along the polymeric chain. The structure of the chain should be examined when the crystallinity of the polymer is to be considered.

Polyethylene is a very simple example of a crystalline polymer. X-ray analysis shows that the chain is extended in a planar zig-zag, at least for long sections, and it is possible to obtain a repeat of all the atoms by operating a 0·255 nm translation along the axis of the chain. This value is called the repeat distance and is easily obtained from the study of X-ray spectra of a stretched polymer fibre, the so-called fibre diagrams. The result obtained by the crystallographic method is perfectly consistent with what is known about the stable conformations of linear hydrocarbons. A succession of *trans* (or 180°) conformations around each carbon-carbon bond leads precisely to such a planar zig-zag structure and the value of the repeat distance

Fig. 86 X-ray diffraction spectra of crystalline isotactic polypropylene (left) and of an amorphous polypropylene. The spectra are registered with a Geiger counter (above) or by photographic techniques. The crystallinity of the samples is revealed by the presence of peaks and spots in well-defined positions.



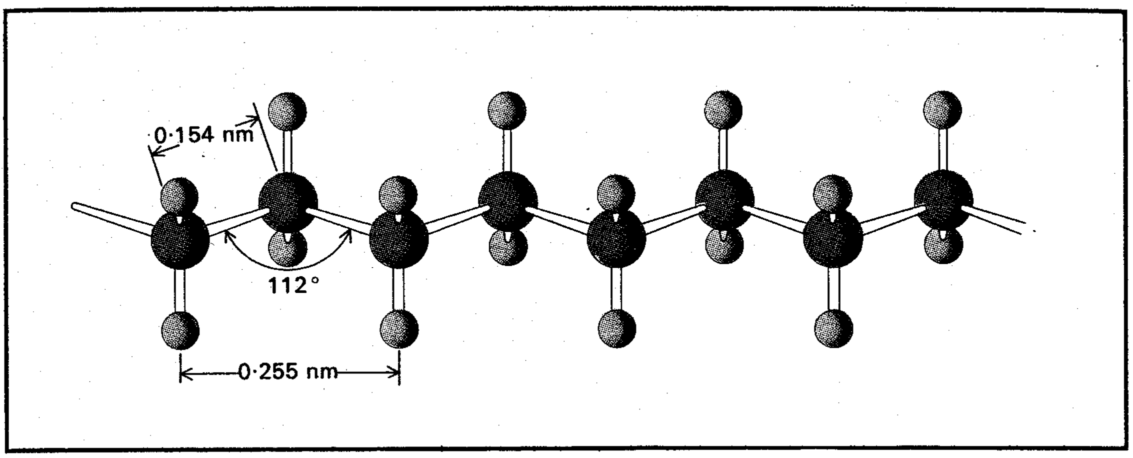


Fig. 87 The conformation of the polyethylene chain in the crystalline state. The internal dihedral angles are 180° (*trans* conformation). The repeat distance, 0·255 nm, agrees with that calculated by using the normal values for the bond lengths and bond angles.

can be calculated to a good approximation, assuming the length of the carbon-carbon bond (0·154 nm) and the value of the C—C—C valency angle (about 110°) (Fig. 87).

The fibre diagram of crystalline polypropylene obtained by the methods described above shows a repeat distance of 0·65 nm; other details of the spectrum indicate the presence of a threefold screw axis (the screw axis is defined by the combination of two symmetry operations: translation along an axis and a rotation of $2\pi/n$ around the same axis); moreover, the experimental density is in agreement with that calculated if one assumes the existence of three monomeric units for each repeat distance. These three facts allow the structure of the crystalline polypropylene chain to be identified with certainty. The monomeric units must repeat themselves with a simple translation every three units but each of these units is joined to the next with a translation of 1/3 of the repeat distance, followed by a rotation through 1/3 of a full circle ($2\pi/3$). The construction of a model immediately shows that these relationships can be explained by a succession of alternating *gauche* and *trans* (abbreviated to G and T) conformations of the chain. The methyl side-group is thus found in a position outside the tertiary helix in a manner which lowers the intramolecular interactions. Conformational analysis tells us that this model (with 60° and 180° rotation angles) and its optical antipode (with angles of 300° and 180°) are the most stable structures for polymers of this type. The helical conformation of isotactic polypropylene in the crystalline state is shown in Fig. 88.

What type of configuration does polypropylene possess in the polymer? If we unwind the helix of polypropylene, we can obtain physically less stable conformations which are endowed with higher symmetry. The two most interesting are the planar zig-zag (analogous to polyethylene) and the configuration with eclipsed bonds,

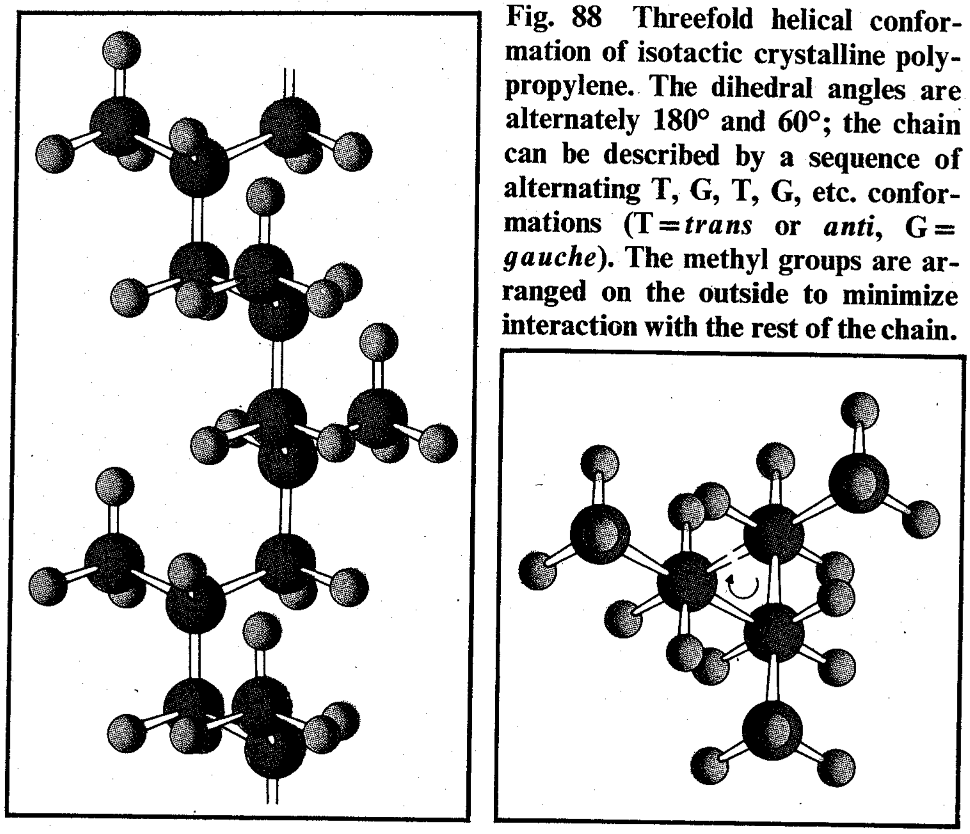


Fig. 88 Threefold helical conformation of isotactic crystalline polypropylene. The dihedral angles are alternately 180° and 60°; the chain can be described by a sequence of alternating T, G, T, G, etc. conformations (T = *trans* or *anti*, G = *gauche*). The methyl groups are arranged on the outside to minimize interaction with the rest of the chain.

corresponding to the Fischer projection (Fig. 89). Both representations illustrate a further structural regularity; the methyl side-group is always on the same side of the chain. Polymers with this characteristic are called isotactic.

We see how far we are from the time of Emil Fischer. The starting-point then was research on configuration whereas today it is determination of the conformation. Configurational analysis has not lost its importance but it is a generalization of the structure rather than a primary object of research. The reason for this evolution is directly tied to the different techniques of investigation used today; these furnish the molecular conformation as an immediately accessible piece of data (diffraction methods are particularly suited for this). The term 'isotactic' has become widely used. It is not easy – perhaps impossible – to define a structure of this type by the conventions of classical organic chemistry.

In addition to polypropylene, many other polymers have been obtained with an isotactic structure (polybutene, polystyrene, etc.) but it was very quickly recognized that certain of these polymers were endowed with different structural characteristics. Among the most interesting are the syndiotactic polymers in which, if the chain is drawn in the zig-zag conformation or in a Fischer projection, the side-chain substituent is found alternately on either side of the chain (Fig. 89).

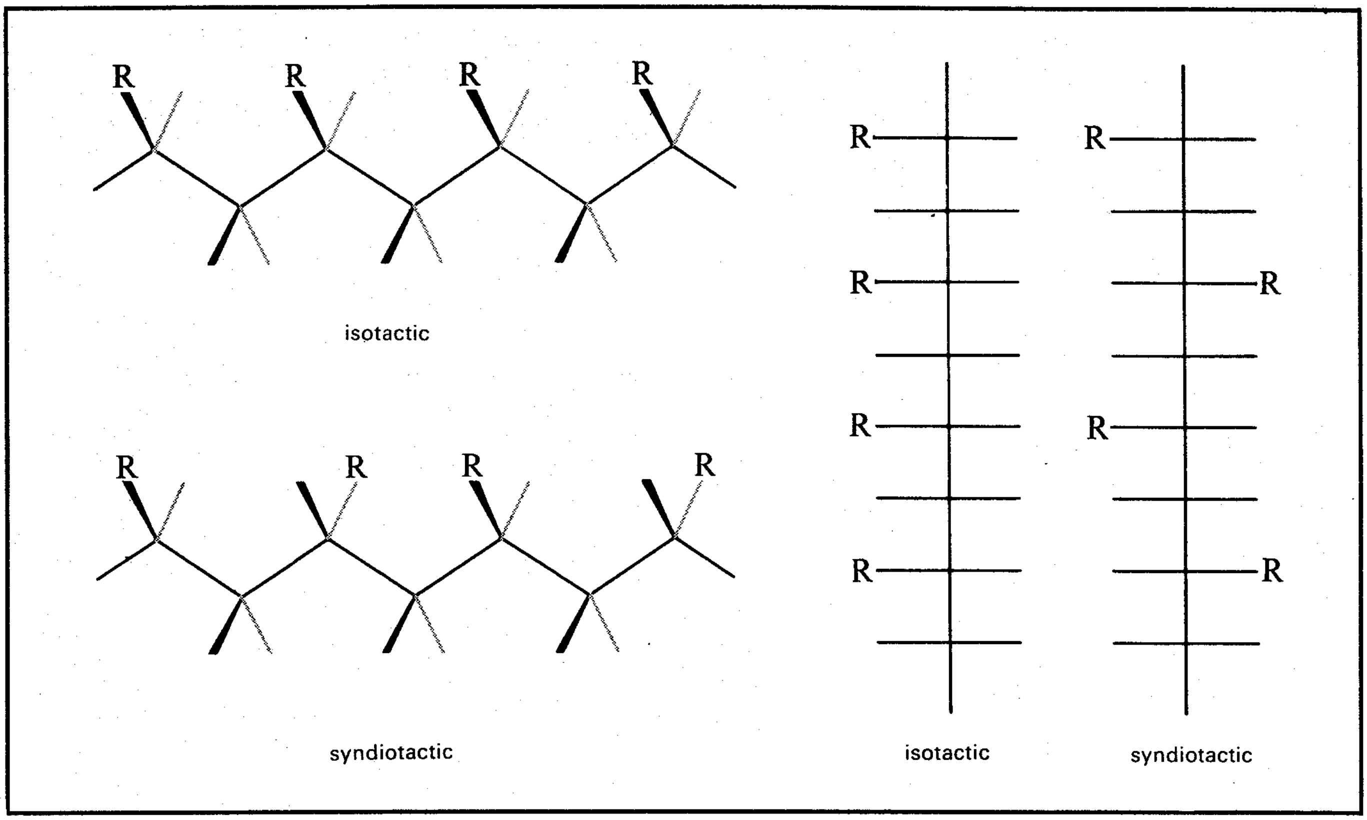
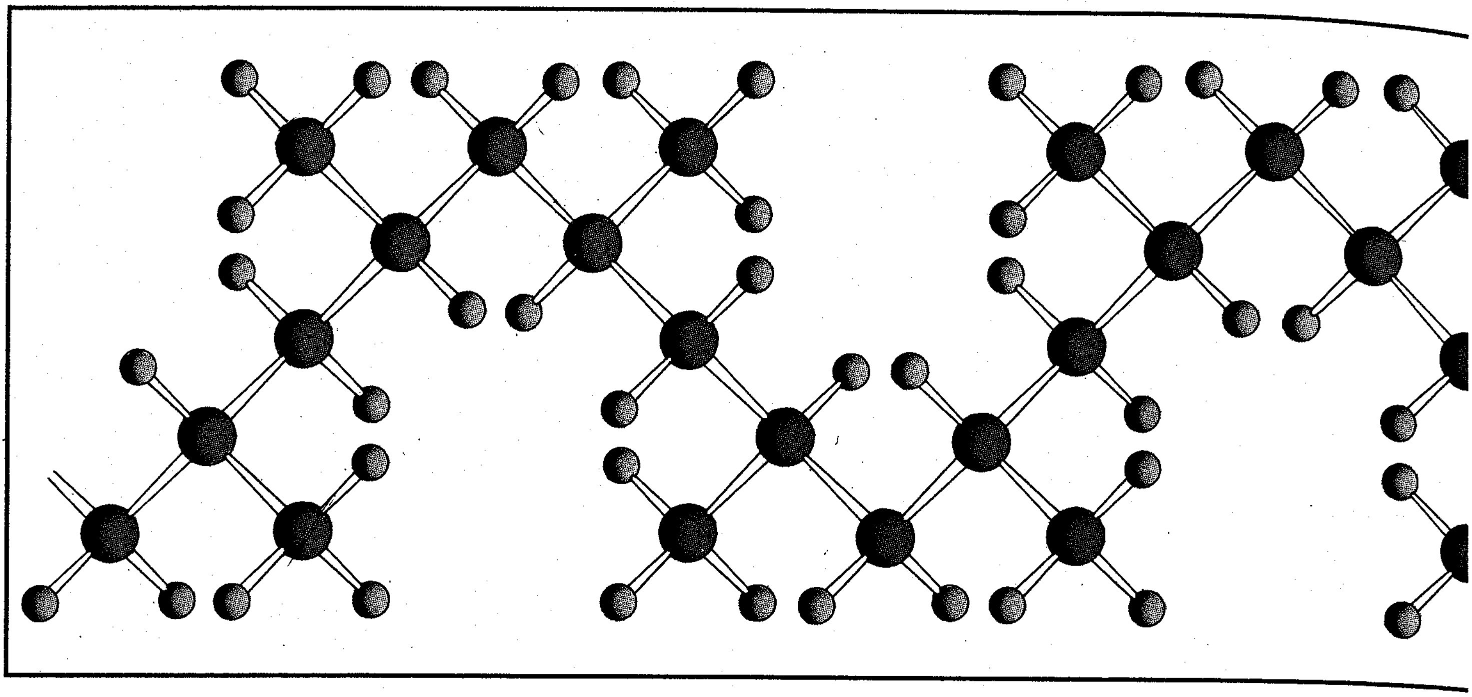


Fig. 89 The configurational relationships within the polymer are clarified by extending the chain into a planar zig-zag or a Fischer projection. In isotactic polymers substituents are always on the same side; in syndiotactic polymers they are found alternately on either side of the chain.

This alternate arrangement was first found in one of the butadiene polymers and later in certain samples of polypropylene obtained under particular conditions: at low temperatures (−70°C) and using different organometallic catalysts. In the first example the shape of the chain, determined by X-ray analysis, was very similar to that of a planar zig-zag and the syndiotactic arrangement was clearly visible; in the second, instead, the chain assumed a complex helical form and only by unwinding it did the configurational type become evident (Fig. 90). Two crystalline structures of syndiotactic polypropylene are now known, the second being similar to that of polybutadiene. Conformational analysis tells us that the energy of the two forms is practically equal and the preference of one over the other arises only from secondary factors related to interactions between neighbouring molecules.

Stereospecific polymerization

In the years which followed the discovery of the first crystalline polymers, hundreds of new polymers were prepared and studied.



The majority of these products are of the isotactic type, but there is no lack of other possibilities. Isotactic and syndiotactic, in fact, define the simplest cases but they are not the only forms of macromolecular stereoisomerism.

In the case of butadiene, four stereoregular polymers were predicted and all were soon afterwards prepared (Fig. 91). Butadiene is a compound containing two double bonds and can react as a simple olefine (it is then said to react in the 1–2 fashion) or in a more complex way (1–4 reaction). In the first case, two polymers of the isotactic and syndiotactic types are obtained. When, however, the reaction is 1–4 i.e., the molecule becomes bonded in the chain through the first and last carbon atoms, each monomeric unit of the principal chain contains a double bond around which exists the possibility of *cis-trans* isomerism. The 1,4-*cis* and 1,4-*trans* polybutadienes have quite different physical properties. The first is an excellent rubber while the second is a high-melting and almost inelastic crystal. There is a surprising analogy with nature here. The rubber obtained from *Hevea brasiliensis* and gutta-percha have the same composition as each other (two polyisoprenes are concerned in this case) but quite different properties. The reason for the different behaviour is again to be found in *cis-trans* isomerism. Natural rubber is the 1,4-*cis*-polyisoprene while gutta-percha is the *trans* isomer.

In 1958, using propylene molecules containing deuterium atoms in specific positions, the first di-isotactic polymers were obtained. Monomeric units contain two different substituents (deuterium atoms and methyl groups) and each of them is arranged in an

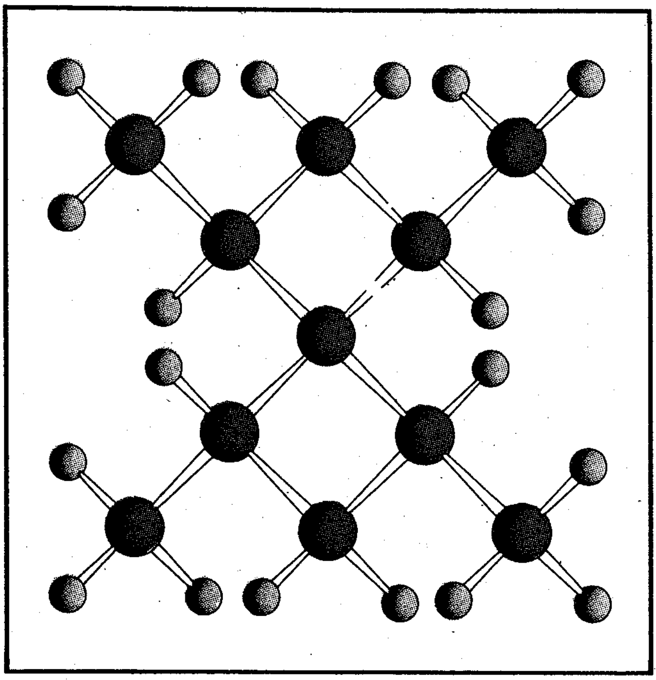


Fig. 90 The complex conformation of the syndiotactic polypropylene chain. Apart from this helical form there is also a planar, zig-zag structure.

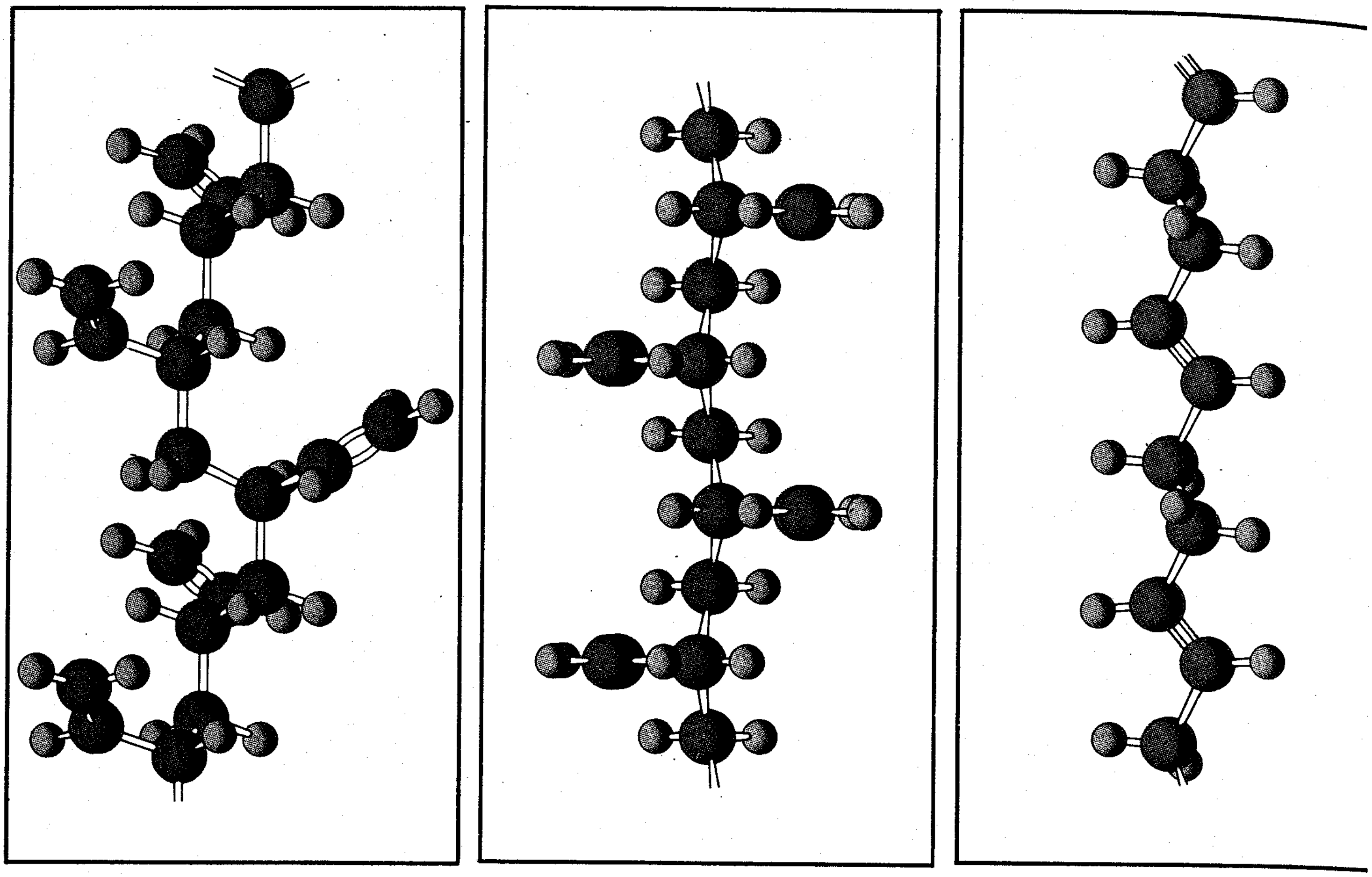
isotactic manner in the polymer, i.e., always occupies the same position with respect to the chain and the other substituents (Fig. 92). Numerous polytactic polymers followed. One can combine the various iso-syndio possibilities with the *cis-trans* isomerism of the butadienes and thus obtain more complex structures.

The results thus indicated are very important in the interpretation of the mechanisms of polymerization. Polymerization is basically an addition reaction repeated many times and it can be studied by applying the criteria described in chapter V. Our experiments have shown that in the majority of cases the addition follows a *cis* steric pathway (as in the oxidation of olefines by permanganate) and required the assumption of a quasi-cyclic mechanism, or at least a close interaction, between the growing chain, the organometallic catalyst and the reacting monomer.

The degree of stereospecificity of polymerizations is very high; (spectroscopic examination indicates that it may be greater than 99 per cent in some cases). One might well ask the reason for this regularity; it is much greater than that met in the great majority of organic reactions.

From the geometrical point of view, the matter is quite clear. Propylene and many other monomers are prochiral (see page 139), that is to say they can be divided into two halves which are mirror images of each other. A left and right face can thus be distinguished. A polyaddition which always occurs on the same face leads to an isotactic polymer; but if the addition occurs on alternate faces, the resulting polymer is syndiotactic (Fig. 93).

To provide a physical explanation for this high stereospecificity,



however, is much less easy. Two hypotheses have been put forward. One explanation is that the regularity of the structure is attributable to an asymmetric induction exercised by the polymeric chain. This latter contains numerous asymmetric carbon atoms and, from the phenomena of diastereoisomerism already described in the preceding chapter, one can predict that one of the two repetitions – isotactic or syndiotactic – must be favoured relative to the other under a given set of experimental conditions. Choice of solvent, temperature or catalyst are all factors which help to determine a particular reaction mechanism; but the determining event from the stereochemical point of view would be the direct participation of the growing chain in the transition state.

According to the second hypothesis the steric regularity is attributed instead to the catalyst. The best catalytic systems for the polymerization of propylene are heterogeneous, i.e., contain some insoluble crystalline compounds (such as titanium trichloride) on whose surface the reaction occurs. In the α form of titanium trichloride each titanium atom is surrounded by 6 chlorine atoms and each of these is bonded to two different titanium atoms in such a way as to produce a local symmetry of the $\mathbf{D}_3$ type. In this symmetry group there are no alternating symmetry axes and this, we recall, is the con-

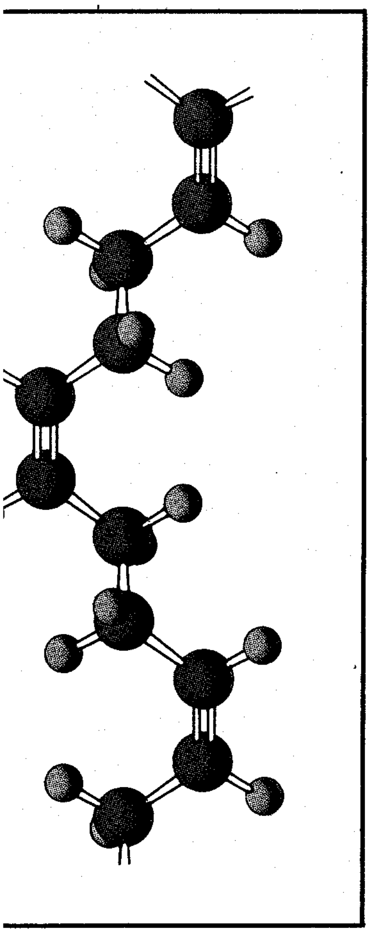


Fig. 91 The four stereoregular polybutadienes: 1,2-isotactic polybutadiene (with a threefold helix), 1,2-syndiotactic polybutadiene (with an approximately planar zig-zag), 1,4-*trans* polybutadiene (structure similar to that of gutta-percha) and, finally, 1,4-*cis* polybutadiene (similar to natural rubber).

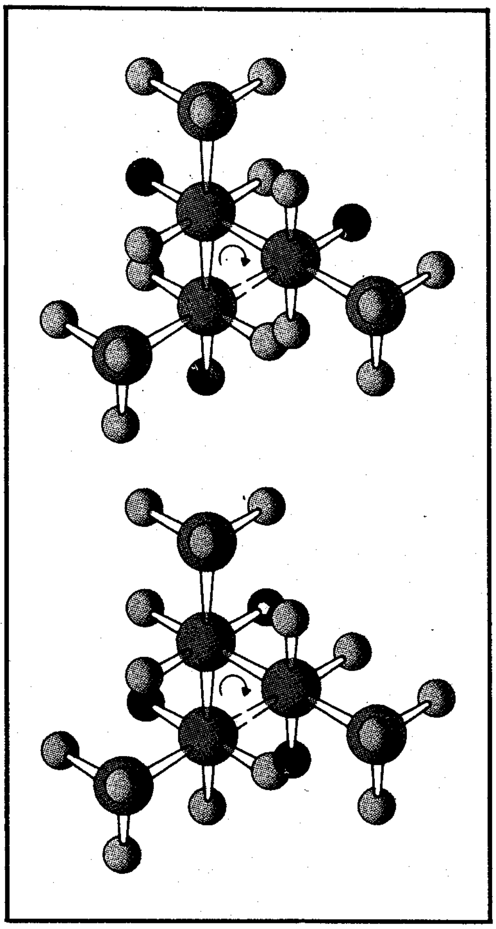


Fig. 92 The simplest examples of di-isotactic polymers (with a doubly isotactic structure) are obtained by introducing into the propylene molecule deuterium atoms in definite positions. (Indicated by the black spheres.) The two *erythro* and *threo*-di-isotactic polymers have different spectroscopic properties owing to the different regular arrangement of the deuterium atoms.

dition which permits the existence of optically active enantiomorphs (Fig. 94). The atoms of titanium are alternatively of the D and L type and co-ordination of the monomer to one of these atoms (for example, to that of sign D) will occur preferentially with one of the two faces (right or left). The successive incorporation of the co-ordinated monomer into the polymeric chain transforms the prochirality of the propylene into an effective asymmetry. If the co-ordination always occurs on the same titanium atom, or on atoms of the same sign, the relative arrangement of the substituents in the polymer will always be equivalent and the resulting polymer will be isotactic.

Each of the two hypotheses is probably true in some particular cases but the conclusions cannot be easily generalized over the many different situations. It is also possible that the two factors, asymmetric induction due to the chain or to the catalyst, coexist and, at least in some cases, are both operative. The final answer may perhaps be obtained from an examination of disordered polymeric structures or from those only partially ordered (such polymers being called atactic and stereoblock, respectively). The type of steric irregularities and their distribution along the chain depend on the polymerization mechanism. But this problem is today still at the limits of the experimental techniques.

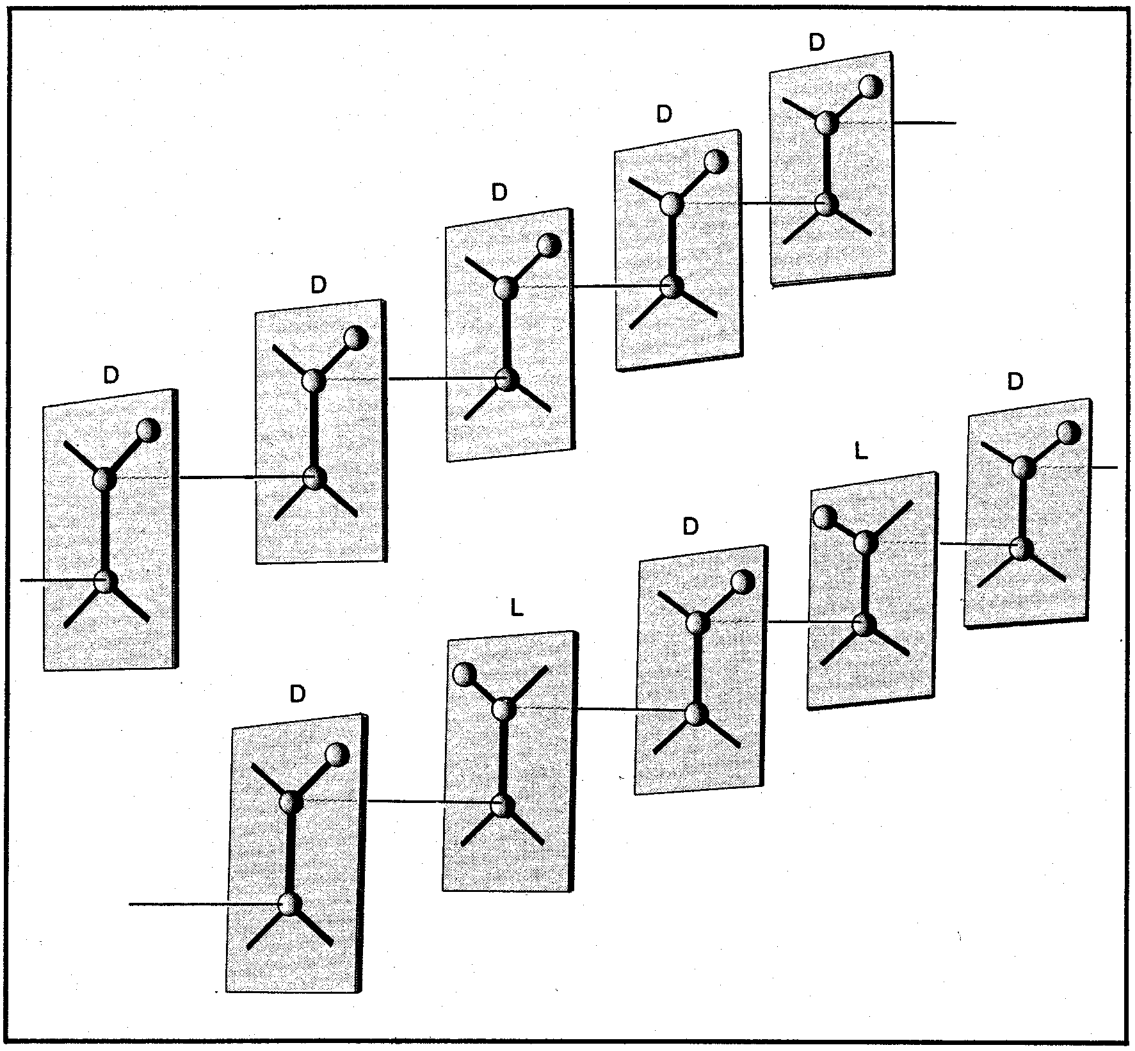


Fig. 93 **The stereochemistry of polymerization can be explained in terms of two parameters: the type of addition to the double bond (*cis* or *trans*) and the way in which the monomer is presented to the growing chain. Propylene and the other vinylic monomers are prochiral. If the monomer always reacts with the same face, the resulting polymer is isotactic; alternatively, if it reacts with both faces, the resulting polymer is syndiotactic. An example of this effect is indicated above with a *trans* type of addition.**

The mechanical properties of polymers

When a solution of a polymer is left to crystallize slowly, one obtains marvellous, extremely thin crystals with a hexagonal shape, visible under the electron microscope (Fig. 95). Contrary to what one would think, the polymer chains are arranged along a hexagonal axis which coincides with the shortest dimension of the crystal. The chains go from one extremity to the other and are folded back on themselves several times in concertina fashion.

The interpretation of the structure of crystallites in a sheet of a polymer obtained by less refined methods (those used industrially) is more complex and not unequivocal. One of the current hypotheses is that different crystallites are formed in different ways, some intermolecularly and some intramolecularly (Fig. 96). The crystal-

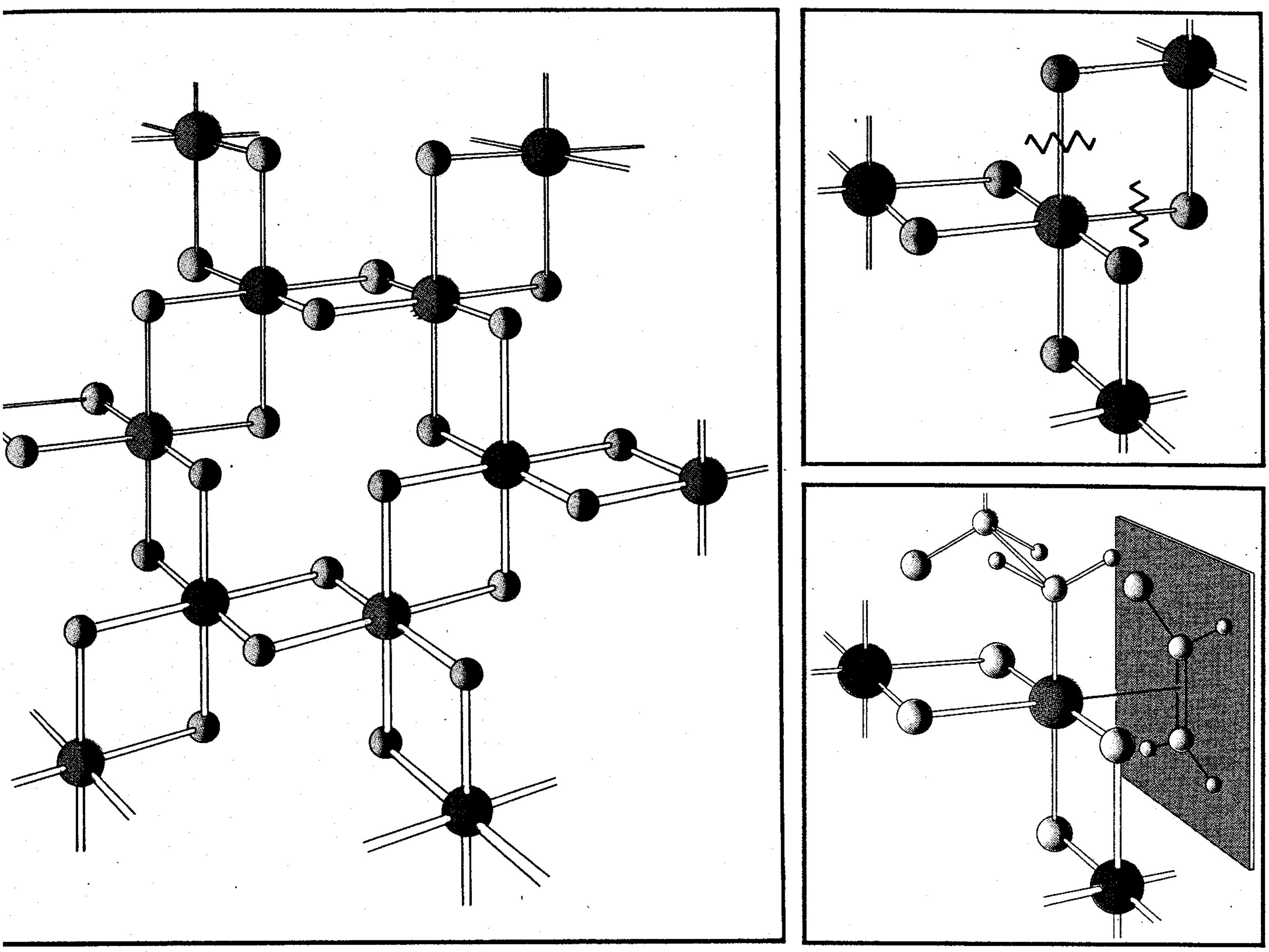


Fig. 94 A fragment of the crystalline structure of α titanium trichloride. The structure is locally dissymmetric, with alternate atoms having opposite signs (indicated by lighter and darker spheres). The extremely high steric regularity of isotactic polypropylene may be derived from the fact that each chain grows on a titanium atom having a given configurational sign and that the monomer always co-ordinates to such an atom with the same face.

lites are randomly arranged and orientated; between one crystal and another there are amorphous zones. When, however, the sheet is stretched along one of its long dimensions, the chains glide over one another irreversibly so as to orientate the crystallites along the direction of the stretching. A sheet thus orientated has a resistance to deformation much greater than that of the original. Further stretching within certain limits is reversible, i.e., when the force is removed, the deformation is reabsorbed by the elasticity of the chain. If the force, however, is too large and exceeds the cohesion between the molecules, they separate and the sheet is broken (Fig. 97).

The cohesion between the molecules is much greater when these form a crystalline lattice than when they are arranged randomly in a more or less amorphous state. The mechanical properties of crystalline

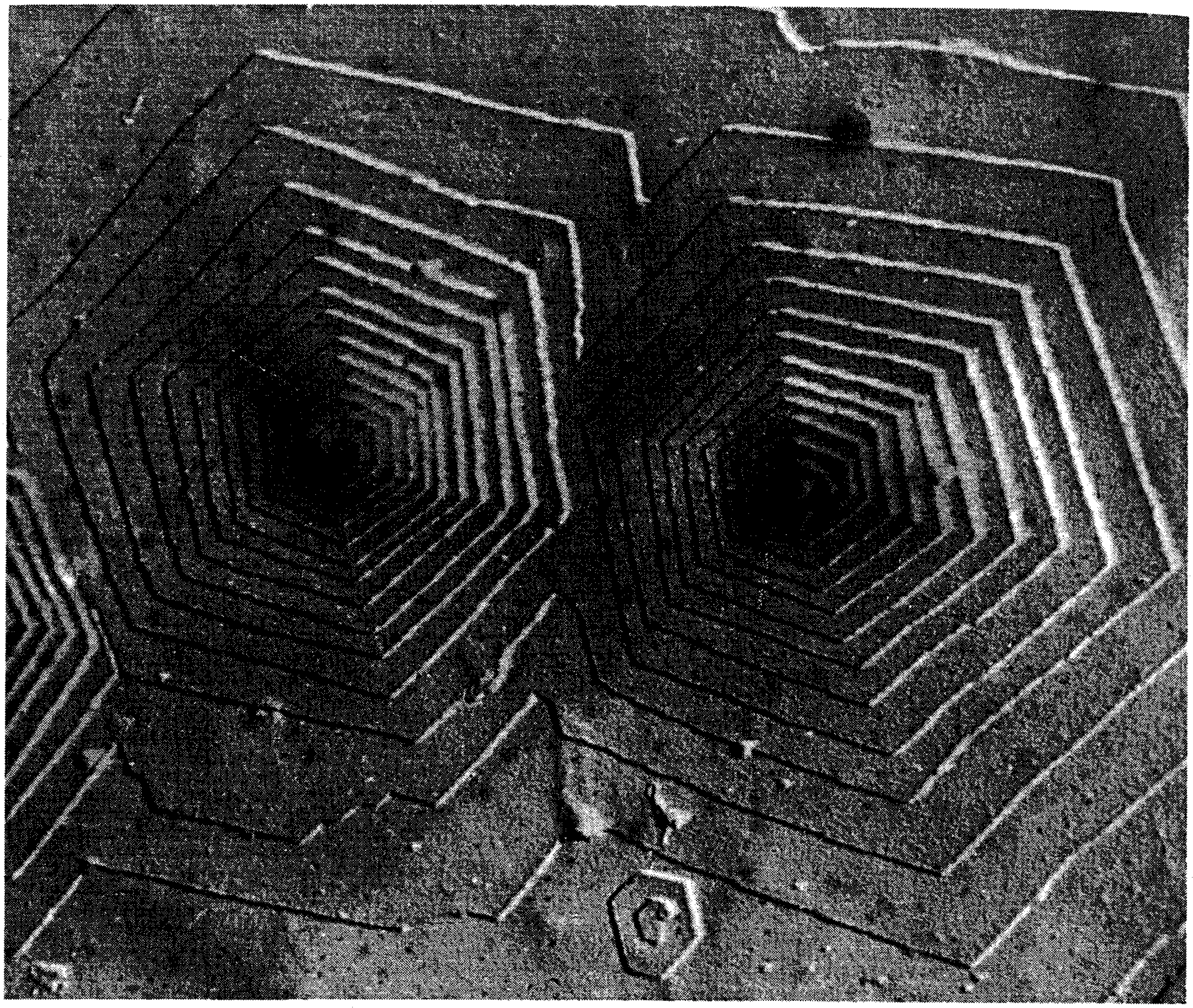


Fig. 95 **An electron micrograph of a single crystal of polyoxymethylene. Contrary to what might be expected, the macromolecules are arranged at right angles to the plane of maximum extension of the crystal. (*Photo*: *General Electric Company*.)**

polymers are therefore different and normally superior to those of amorphous polymers of the same chemical composition. The differences concern such apparently very diverse properties, such as breaking load, solubility and melting point, but all can be associated with the same factor: the stability of the crystalline structure and the forces of molecular cohesion. The greater the crystallinity of the polymer – other things being equal – the higher will be its breaking load (i.e., the greater will be the force necessary to break the sample), the lower the solubility (owing to the greater work the solvent must do in order to separate the molecules and reduce them to a disordered state) and the higher the melting point. These two phenomena, solution and melting, are closely related: melting can, in fact, be considered as a solution of the solid polymer in the same polymer already liquefied.

For an amorphous polymer, a melting point cannot strictly be defined. The transition from an apparently solid state to a liquid does not occur in a discontinuous manner but with a progressive diminution of the viscosity. Instead it is possible to define a glass transition point below which the amorphous polymer is fragile and breaks easily when subjected to a dynamic force. Above this point its behaviour is elastic or viscous, depending on whether or not the deformation is reversible. The difference in behaviour is related in part to the molecular weight which must be particularly high for elastic behaviour to be observed.

When it is wished to improve the elastic behaviour of a polymer, that is to say, to make possible a large, easily reversible lengthening and, simultaneously, a notable resistance at maximum extension, it is necessary to use products having melting points or glass transition temperatures below the temperature at which they will be employed.

Good elastic behaviour occurs in certain homopolymers, like 1,4-*cis*-polyisoprene (or natural rubber) and 1,4-*cis*-polybutadiene, or it can be obtained through copolymerization, i.e., by mixing two different monomers before polymerization. For example, the copolymer from ethylene and propylene is a good rubber; moreover, its characteristics can be modified by varying the relative proportions of the monomers. The mechanical properties of the copolymer are not intermediate between those of the two homopolymers, polyethylene and polypropylene, but are strongly influenced by the irregularities introduced into the structure completely destroying its crystalline nature.

The behaviour of a rubber notably improves if irreversible viscous movements can be reduced. The gliding of one macromolecule over another can be prevented by hooking the molecules together at points with chemical bonds. This is the basis of vulcanization, a process in which the addition of sulphur and other compounds allows the conversion of a potential elastomer into a rubber of industrial interest.

The manufacture of thermoplastics generally consists of melting or solution in suitable solvents followed by working into objects: threads, strips, stamped articles and so on. Macromolecules, when in the fluid state, also differ radically from compounds of low molecular weight in their high viscosity. To this is related, for example, their ability to form filaments which, once solidified and stretched, constitute the well known synthetic fibres (Nylon, Orlon, etc.). At the molecular level, the viscosity arises from the great size of the single molecules and from the fact that, in the fluid state, they are tangled together.

Practical issues apart, the study of polymers in the fluid state, and

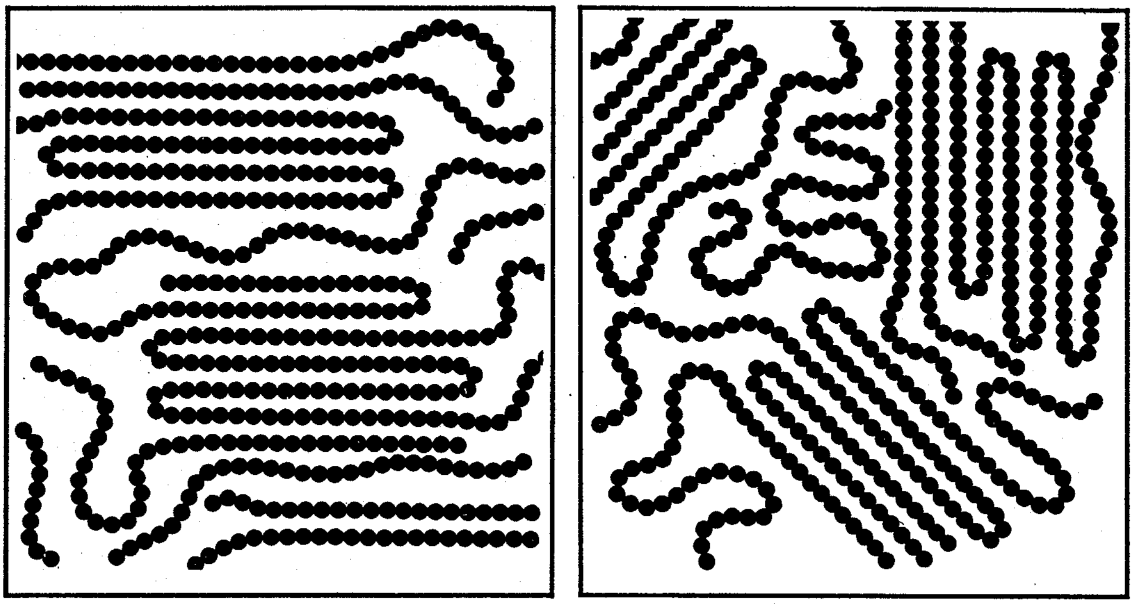


Fig. 96 In partially crystalline sheets there are ordered regions in which the macromolecules are parallel to each other; there are also disordered zones. When the sheet is stretched, the axes of the various crystals are displaced along the direction of the stretching and become parallel to it. The mechanical properties of the polymer improve considerably with this process.

particularly in solution, is very important. This is because information can be obtained concerning the real state of macromolecules in conditions very different from those existing in crystals. In a solvent which does not interact with the polymer the macromolecule assumes a more or less spherical shape similar to a loose ball of wool.

An isotactic polymer, for example polypropylene, possesses a helical conformation in the crystalline state which corresponds to a state of minimum energy. After fusion or solution, however, the disorder of the system increases. The macromolecules separate from one another, fold up again on themselves and assume in some regions conformations different from those typical of the threefold helix. In this process the molecule passes to a state of higher internal energy, but there is an entropy contribution which stabilizes the partially disordered state with respect to the perfectly regular one. The problem is very similar to that of the butane conformations which we discussed in chapter III and is dealt with by using fundamentally analogous methods, even though they may be more complex from the mathematical point of view. Polypropylene in solution does not therefore consist of rigid spirals but neither is it totally disordered. It retains a certain memory of the conformation it had in the crystal. The chain is helical for a certain distance, followed then by inversion, then a small helical segment of the opposite sign, another inversion, and so on. The number of inversions of the sense of the helix increases in a continuous way with an

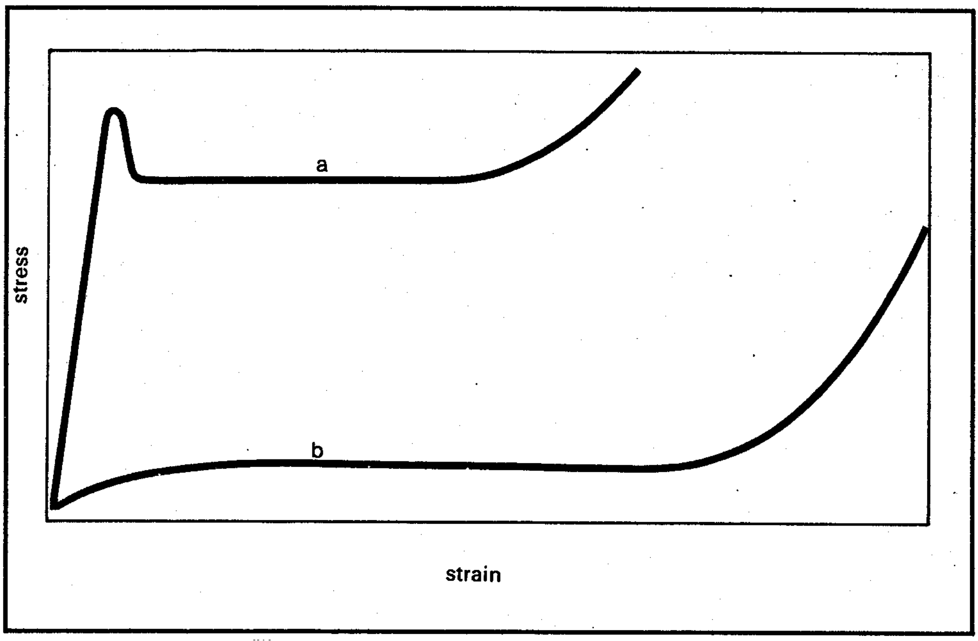


Fig. 97 **The mechanical properties of different types of polymers are illustrated in this stress-strain diagram. It shows the typical behaviour of a crystalline polymer (*a*), and a rubber (*b*). The maximum breaking load is observed for crystalline products while the maximum lengthening is found in rubbers.**

increase in temperature. There is also an increase in the conformational disorder. This description is in agreement with the data which may be obtained, by different techniques, from isotactic polymers. Among these, the study of optically active polymers derived from the α-olefines (with the general formula $R^* - CH = CH_2$, where R^* represents a chiral group) is particularly important. The value of the optical activity and its variation with temperature, or with the wave-length of the light used in the measurement (typical stereochemical methods), can be related to particular local conformations of the polymer, from which it is possible to deduce the shape of the entire macromolecule.

VII

Biological macromolecules

What we have said concerning synthetic macromolecules makes it very much easier to face one of the most beautiful and fascinating problems of chemical research: the study of the structure and properties of polymers of biological origin. As we have already said, a large part of the matter contained in living organisms, both animal and vegetable, is of a macromolecular nature. Only the high molecular weight allows carbon compounds to have sufficient resistance and flexibility to impart mechanical strength, as in the cellulose of plants, or to possess those properties of permeability which allow the regulation of the complex equilibria of water and nutrition of cells and tissues. Moreover, we shall see how the particular complexity of macromolecular structures allows certain conglomerations of atoms to store the information which is the basis of genetic processes.

From the point of view of chemical composition, as also from the structural and functional point of view, the natural polymers are generally divided into four classes: the hydrocarbon polymers, such as rubber and gutta-percha (of which we have already spoken), the carbohydrates, the proteins, and the nucleic acids. Even though the present trend is towards research on the proteins and the nucleic acids (largely because of the importance of the problems concerned), we cannot forget the part played by the carbohydrates, from starch to cellulose, in life on earth.

We have already mentioned glucose. Photosynthesis, the process for producing glucose, and thus all its polymers, from water and carbon dioxide as starting materials, is the most important chemical process in the world. Agriculture, nutrition and many industries depend on it in a direct way. But leaving aside the human economy, sugars and photosynthesis have also played a decisive part in establishing the complex natural equilibrium which now exists. One of the products of photosynthesis is oxygen, the gas essential for respiration. It does not seem likely that oxygen was present in any appreciable quantity in the primeval atmosphere; it must have been largely produced by photosynthesis. We can therefore say that life in the form we know today on Earth, i.e., aerobic life, is doubly associated with the presence of sugars, both as reservoirs of chemical energy and also as oxygen generators.

We shall not enter into the particulars of the biochemical action of natural polymers. We shall try instead to see how the same general rules of structure and chemical dynamics mentioned in the previous pages are valid and applicable in this field, which seems in many ways a mysterious and surprising world in itself.

The polysaccharides

When cellulose and starch are subjected – by means of particular enzymes or through the action of acids – to strong hydrolysis, i.e., hydration accompanied by a breaking of the chain, a well-known product is obtained, D-glucose. This can be considered the fundamental building block, the monomeric unit or basic unit, of the macromolecular structure. Cellulose and starch are both polymers of glucose, or polysaccharides. Why are they so different from each other? Starch is the basis of human foodstuffs while cellulose can neither be digested nor assimilated by man; on the other hand, it furnishes valuable fibres such as cotton and flax, while starch is scarcely crystalline, softens in water and easily forms a paste.

The answer can be given in stereochemical terms by an examination of the two substances. If the two polysaccharides are hydrolyzed under mild conditions, two characteristic products are obtained, each consisting of glucose molecules: cellobiose from cellulose and maltose from starch. These two polysaccharides are derived respectively from β- and α-glucose, the two cyclic forms in which this simple sugar can exist (Fig. 98). α- and β-glucose are related to each other as diastereoisomers (in sugar nomenclature they are called anomers, a term which is a special case of the more general term, diastereoisomers). The situation is analogous to that already seen for natural rubber and gutta-percha, i.e., 1,4-*cis* and 1,4-*trans*-polyisoprene. In each pair of polymers the monomeric unit is the same, at least with respect to the fundamental chemical structure; the differences only involve the spatial orientation of the various substituents: *cis* or *trans* in the hydrocarbon polymers, and equatorial or axial in cellulose and starch.

Structural investigation carried out with the most modern techniques (X-ray analysis, nuclear magnetic resonance, infrared spectroscopy) on cellulose and starch and their derivatives has fully

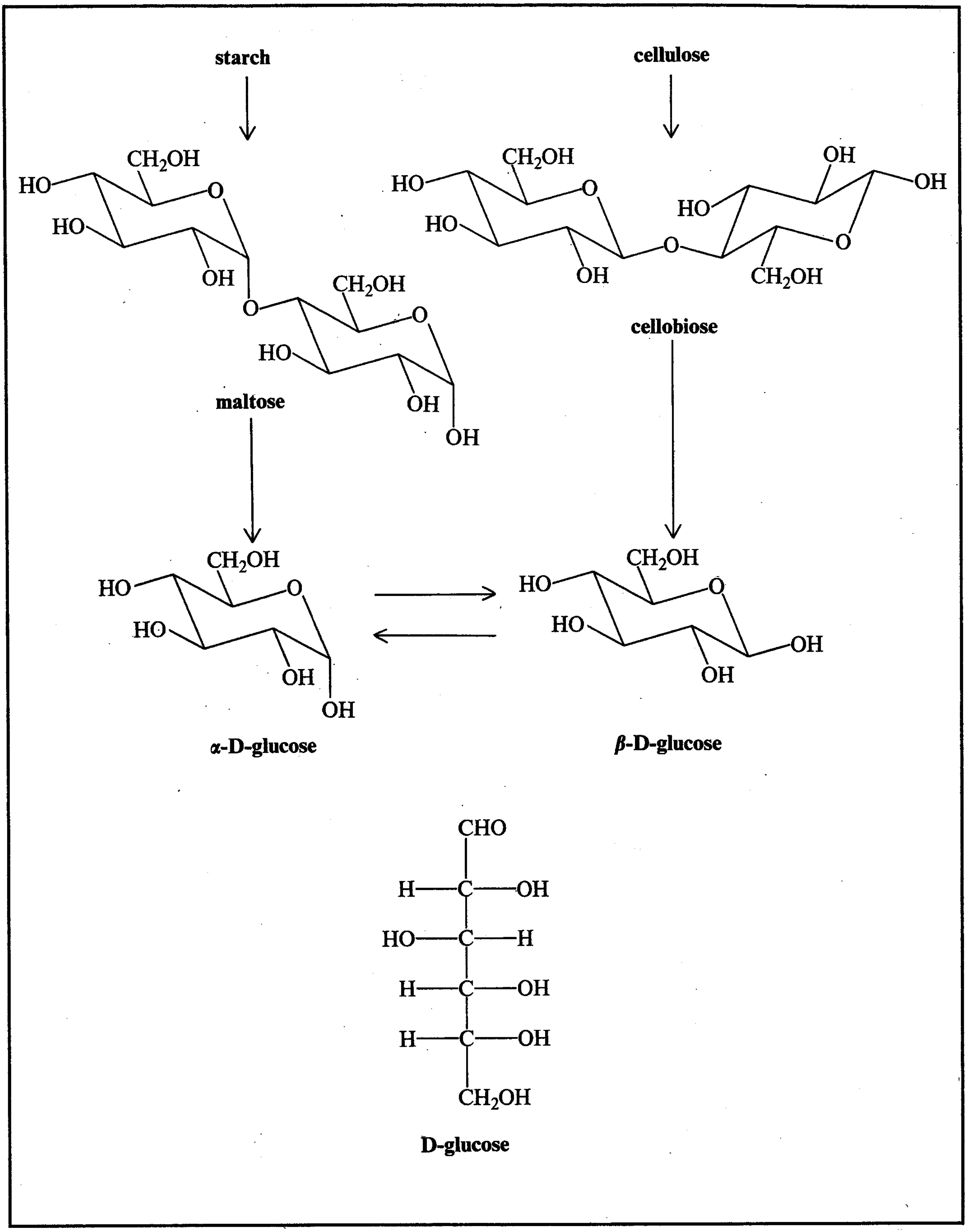


Fig. 98 The degradation of starch and cellulose leads to the same product, D-glucose, through different intermediates. Starch is transformed into maltose, a derivative of α-glucose, while cellulose is changed into cellobiose, itself formed from two β-glucose units; α- and β-glucose easily convert in solution.

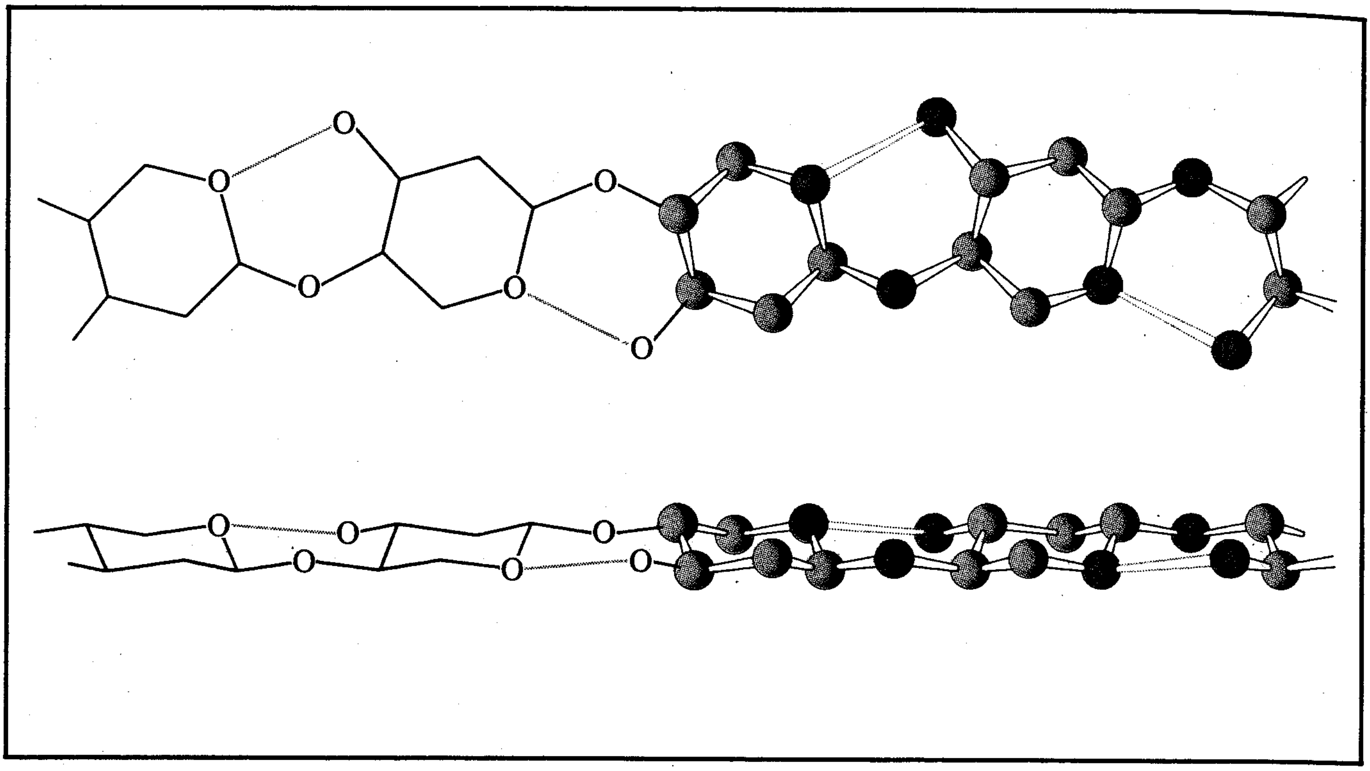


Fig. 99 One of the structures proposed for cellulose. The black bonds are covalent and the lighter ones are hydrogen bonds. The glucosidic rings, viewed perpendicularly from above in the upper drawing, actually exist in the chair conformation.

confirmed the dualism just described and has allowed the reason for the different behaviour to be understood.

Cellulose consists of a succession of β-glucosidic rings in the chair conformation with all the substituents in the equatorial positions. The rigidity and particular resistance of the fibres is due to the fact that in reality there is a double linkage between the successive monomeric units. One linkage is formed from covalent bonds and the other from hydrogen bonds (Fig. 99). This latter type of bond is very common in biological systems (we shall see that it plays a fundamental part in the structure of proteins and nucleic acids) and is established between the hydrogen atoms of -OH and -NH groups and other strongly electronegative atoms like oxygen, fluorine, chlorine, nitrogen, etc. While the energy involved in hydrogen bonds is relatively small with respect to that of the covalent bonds (from 2 to 10 Kcals per mole against 20 – 100) its presence or absence is a determining factor in the stereochemical field, where the difference in energy between the different conformations is of the order of a few kilocalories or even less. A fundamental condition for the formation of these bonds is that the distance between the two atoms connected by the hydrogen bridge should be quite small, between 0·2 and 0·3 nm. In cellulose, rotation of one glucosidic ring with respect to the next would lead to a separation of certain atoms and

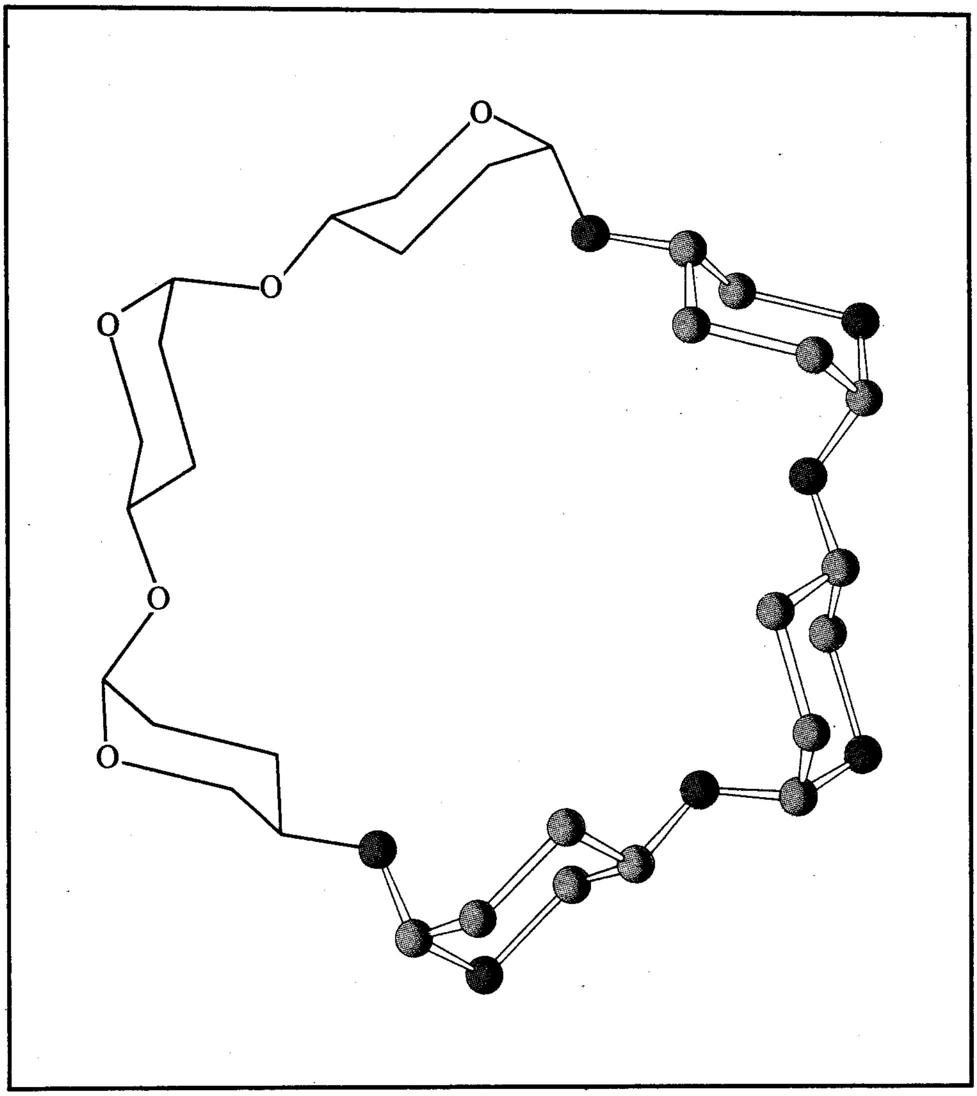


Fig. 100 Cyclodextrin and α-amylose are closely related both chemically and structurally. The first is a cyclic compound, containing six α-glucosidic residues; the second is a macromolecule with a helical shape whose projection on a plane is practically identical with that of cyclodextrine. The superposition of cyclodextrin molecules gives rise to a channel inside which other molecules can be trapped.

the breaking of hydrogen bonds; this rotation is therefore strongly resisted. This explains, at least in part, the mechanical resistance of the cellulose fibres.

As far as starch is concerned the situation is much less clear-cut. The starch of potatoes or rice consists of two principal substances, α-amylose and β-amylose (amylopectin), both polymers of α-glucose, but the first has a linear structure while that of the second is branched. Since it is less complex, research has been directed mainly at the former. α-amylose, however, exists in at least three crystalline forms, and the structures of these are still not completely known.

Among them, the form V is particularly curious since it consists of a large helix in which the interior can be filled with other smaller molecules, such as iodine, various organic compounds, mineral salts, water and so on. Such addition (or more properly, inclusion) compounds are also formed by other carbohydrates such as cyclodextrin, a cyclic oligomer of α-glucose (the term oligomer referring to a short polymer, formed from 3–20 monomeric units) which has been found a very useful model of the amylose structure (Fig. 100).

During the last two decades, the structure of amylose has been the subject of a controversy over the conformation of the α-glucosidic ring, a controversy which has only been resolved in recent years. At the heart of the problem was the attempt to explain the numerous structures of amylose and their ready interconversion. An elegant way of solving the problem seemed the hypothesis of a boat conformation for the α-glucosidic ring. It will be remembered that in the case of cyclohexane this form was not taken into account owing to its high energy content and low stability. However, it has very low internal rotation barriers and can easily be transformed into other boat forms; for this reason it is also called a flexible or mobile form of cyclohexane. Substitution of a CH_2 group by an oxygen atom (i.e., the change from cyclohexane to pyran and thus to the sugars should not alter the flexibility of this form but rather should lessen its instability with respect to the chair form. This hypothesis and some rather ambiguous experimental work led into a blind alley from which a way out was only recently found using crystallography and spectroscopy. Today we know that the α-glucosidic ring is a chair with four equatorial substituents and one axial, fully conforming to the conformational rules for cyclic compounds already enunciated. This fundamental point having been established, a correct study of the various forms of α-amylose was possible. These forms are not due to different conformations of the sugar ring but rather to a different orientation of successive units and thus to a different arrangement of the hydrogen bonds along the individual chain and between neighbouring chains.

The structures of proteins

The difficulties to be faced in solving some biochemical problems are immense and sometimes even insurmountable at a particular stage of research. The possibility of choice is here rather more limited than in synthetic chemistry, where it is possible – more or less – to construct at will the most suitable model to verify the current theories. Nature instead offers for our study the product of a biological evolution which certainly did not have as a final object its ease of study by man. The situation is often resolved through the intuitions of brilliant workers (such as Pauling's α-helix or Watson and Crick's pairing of the bases), but more often by improvements in the techniques of investigation. For example, the powerful work of Perutz on haemoglobin would have been quite impossible without the use of the most modern methods.

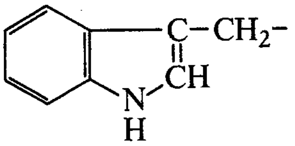
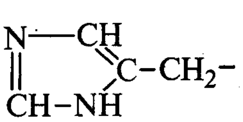
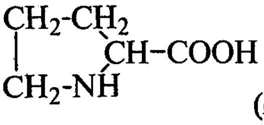
Among the most important and difficult problems to solve is without doubt that of the structure of proteins. The most varied types of protein exist, each with its specific biological action; and research on their structures is an essential factor for the detailed study of their function at the molecular level. The proteins are compounds with important biological functions but, in spite of their complexity, protein and enzymic reactions must be reduced to chemical formulations. In this study chemistry meets biology. The same problems are faced with different methods and mentality and it cannot be denied that there is considerable misunderstanding and ambiguity between the two schools. But the initial difficulties having been overcome, modern biochemistry was born from this union and it is this study which deals explicitly with biological phenomena at the molecular level. To make the change of methods and problems more evident, it is often called molecular biology or, for that very large part dealing with proteins and nucleic acids, macromolecular biology.

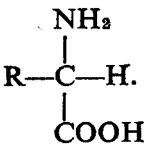
Proteins are macromolecules with molecular weights varying from a few thousand to several million. They are formed from many amino acids joined together by amide linkages. They are in fact copolymers for they contain twenty different types of amino acid (Tab. V). The percentages of the various amino acids and, furthermore, their distribution along the chain, are characteristic of each protein. Although apparently random, this distribution hides an order and purpose not completely understood. The experimental determination of amino acid sequences, the so-called primary structure of a protein, still represents a major difficulty even with the great help provided by instrumental analysis (Fig. 101).

An important observation of a stereochemical nature is already possible. All the amino acids, with the exception of the simplest, glycine, possess an asymmetric carbon atom. Of the two possible optical antipodes, only one is found after the hydrolysis of proteins. Still more interesting is the fact that the configuration is the same for all the amino acids. This phrase must be understood thus: if we fix the carboxyl group, the asymmetric atom and the amino group in space, the radical R – that radical which characterizes the individual amino acid – is always placed on the same side with the hydrogen atom opposite to it. This result may seem surprising at first sight but it is neither accidental nor very strange. We have already said that many natural organic products are characterized by a very high stereochemical homogeneity and we indicated the existence of exclusive enantiomeric series for entire groups of compounds (for example, the D series of the sugars and this L series of the amino acids).

The reason for an identical configuration is not clear until one examines the secondary structure of proteins, i.e., the conformations of the successive amino acid residues. In this respect, one cannot do other than cite the name of Linus Pauling, a unique figure in mankind and science, the receiver of two Nobel prizes, one for peace and the other for chemistry. Pauling, who in the 1930s was one of the

Table V. The most common natural amino acids*

Name	Abbreviation of the residue	Structure of the group R—
glycine	GLY	H—
alanine	ALA	CH_3—
valine	VAL	$(CH_3)_2CH$—
leucine	LEU	$(CH_3)_2CH—CH_2$—
isoleucine	ILEU	$C_2H_5(CH_3)CH$—
phenylalanine	PHE	$C_6H_5—CH_2$—
serine	SER	CH_2OH—
threonine	THR	$CH_3—CHOH$—
arginine	ARG	$HN{=}C(NH_2)NH—CH_2—CH_2—CH_2$—
aspartic acid	ASP	$HOOC—CH_2$—
asparagine	ASN o ASP—NH_2	$H_2NCO—CH_2$—
glutamic acid	GLU	$HOOC—CH_2—CH_2$—
glutamine	GLN o GLU—NH_2	$H_2NCO—CH_2—CH_2$—
cysteine	CYS	$HS—CH_2$—
methionine	MET	$CH_3—S—CH_2—CH_2$—
lysine	LYS	$H_2N—CH_2—CH_2—CH_2—CH_2$—
tyrosine	TYR	pHO—$C_6H_4—CH_2$—
tryptophan	TRY	
histidine	HIS	
proline	PRO	 (complete formula)



$$R—\overset{\displaystyle NH_2}{\underset{\displaystyle COOH}{C}}—H.$$

* General formula: The abbreviation refers to the repeat unit, —NH—CHR—CO—, in the polypeptide chain. The general formula also expresses the absolute configuration of the natural amino acids. Proline is different from all the other amino acids listed because the R substituent is bifunctional and bonded to the nitrogen by ring formation.

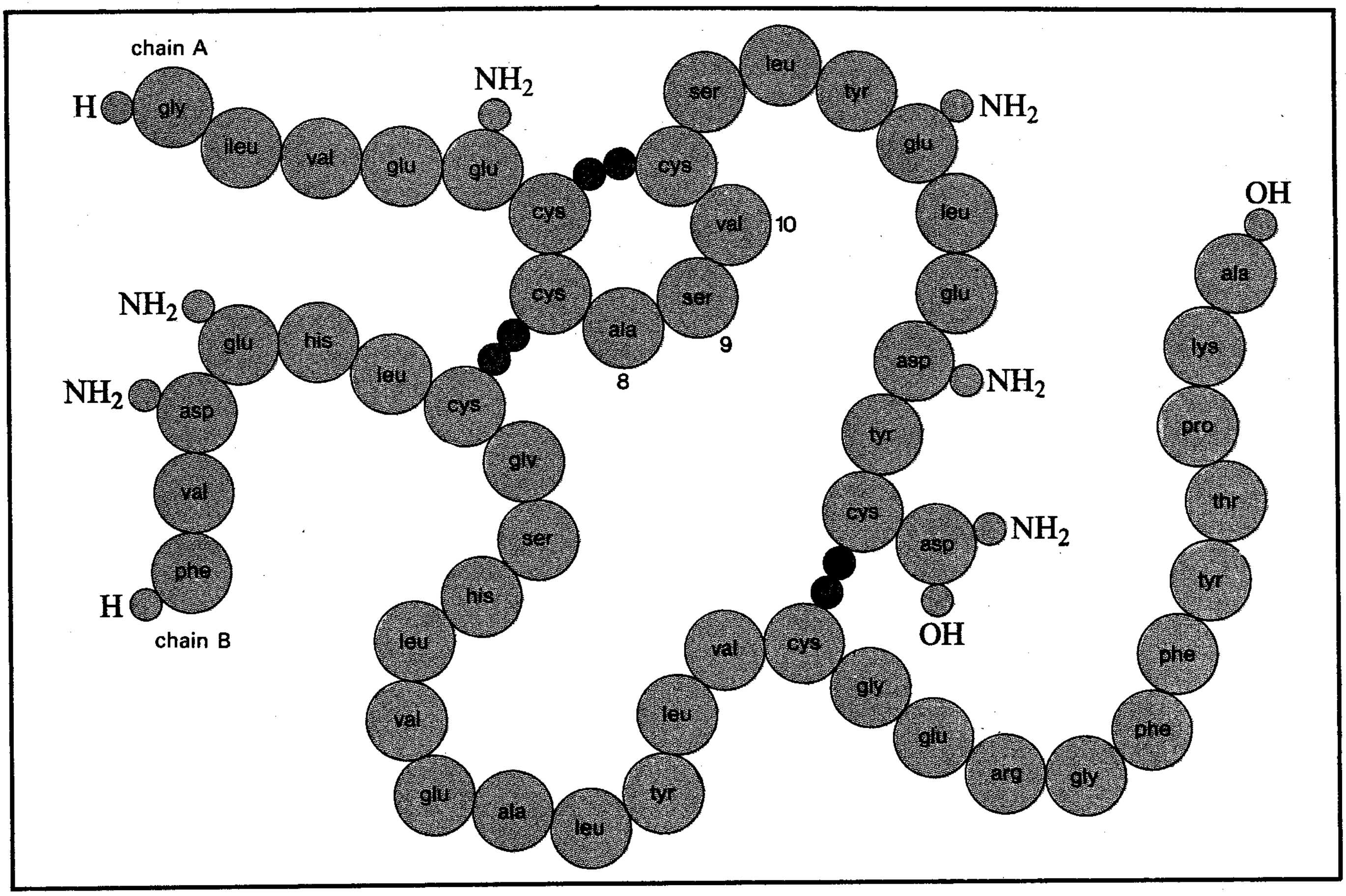


Fig. 101 A conventional representation of the bovine insulin molecule. The large circles represent the individual amino acids, the small light circles the side and terminal groups, and the black circles the sulphur bridges. Insulin, formed from two peptide chains containing respectively 21 and 30 amino acids, was synthesized in recent years by Chinese scientists.

founders of modern valency theory, succeeded in showing that the polypeptide chains, i.e., sequences of amino acids joined end to end, of certain crystalline protein fibres possess a helical structure, given the name α-helix.

The α-helix contains 18 monomeric units in each 5 turns (18/5 helix); for each complete rotation there are thus 3·6 amino acid residues. This particular arrangement of the atoms is strongly stabilized by a net of intramolecular hydrogen bonds. In the polypeptide chains the hydrogen bonds are formed between the -NH group and the -CO of the fourth previous residue which lies almost exactly one rotation under the nitrogen atom (Fig. 102).

A detailed examination of the structure shows that the amide group is planar and that the side groups of the amino acids are found on the outside of the helix in such a way as to interact as little as possible with the rest of the chain. From this point of view, the analogy with the isotactic polymers is very close and one understands why rigorous configurational purity is indispensable for the helix to be stable. The presence of a D amino acid would lead to an increase in the energy of the system, due to the unfavourable arrangement of the side group causing conformational changes.

The polypeptide helix is a typical co-operative system, that is to say, a system in which some properties are different from those predicted by summing the contributions of the individual constituents. These properties disappear or are soon modified when the

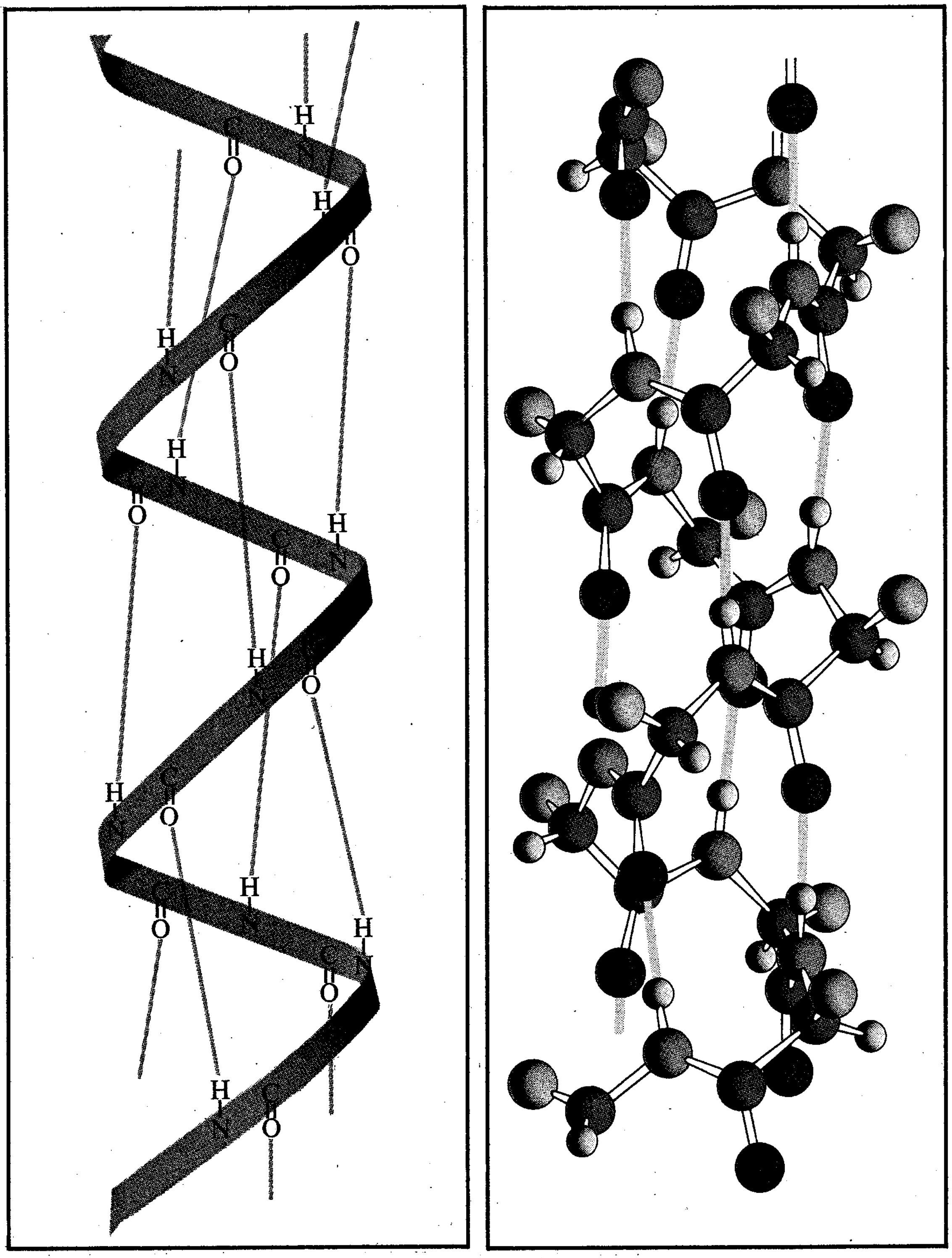


Fig. 102 The most common conformation of polypeptide chains in the crystalline state is Pauling's α-helix. Its stability is due both to the formation of numerous intramolecular hydrogen bonds and to the favourable arrangement of the side groups.

macromolecule loses its helical structure and is transformed into a random coil. The change from a strictly ordered to a disordered form, or vice versa, can occur with a small change of temperature or acidity of the solution; the phenomenon resembles the melting or dissolving of crystals. We have already spoken about the influence of temperature on solutions of synthetic polymers. In that case the conformational modifications are gradual and partial; here the phenomenon is sudden and complete. In other words, a polypeptide chain represents a more highly organized (or co-operative) system than the hydrocarbon polymers previously examined. Moreover, the chain is strongly affected by the influence of solvents, generally water (which participates directly in the stabilization of certain conformations), salt concentration, pH and so on.

Globular proteins

The α-helix represents a stable conformation of polypeptide chains; but the term stable has a very relative sense. The native protein, as it is found in living organisms, easily undergoes, especially under the influence of temperature, irreversible transformations called denaturation. The best known denaturization of a protein consists of the cooking of the white of an egg. In the denaturation process the helical structure disappears and, simultaneously, more complex phenomena occur, such as dehydration, changes in chemical reactivity, and disappearance of the biological properties.

Not all amino acids prefer to assume an α-helical chain. Proline, for example, prefers a planar conformation; glycine, because of its non-dissymmetric structure, has no preference between the α-helix (which has a clockwise sense) and its enantiomorph (anticlockwise). A polypeptide chain made from a sequence of different amino acids can thus present some anomalies with respect to the helical conformation already described. It will have folds and hollows and overall will assume a characteristic form, globular, ovoid, plate-like and so on. This general form is called the tertiary structure of the protein.

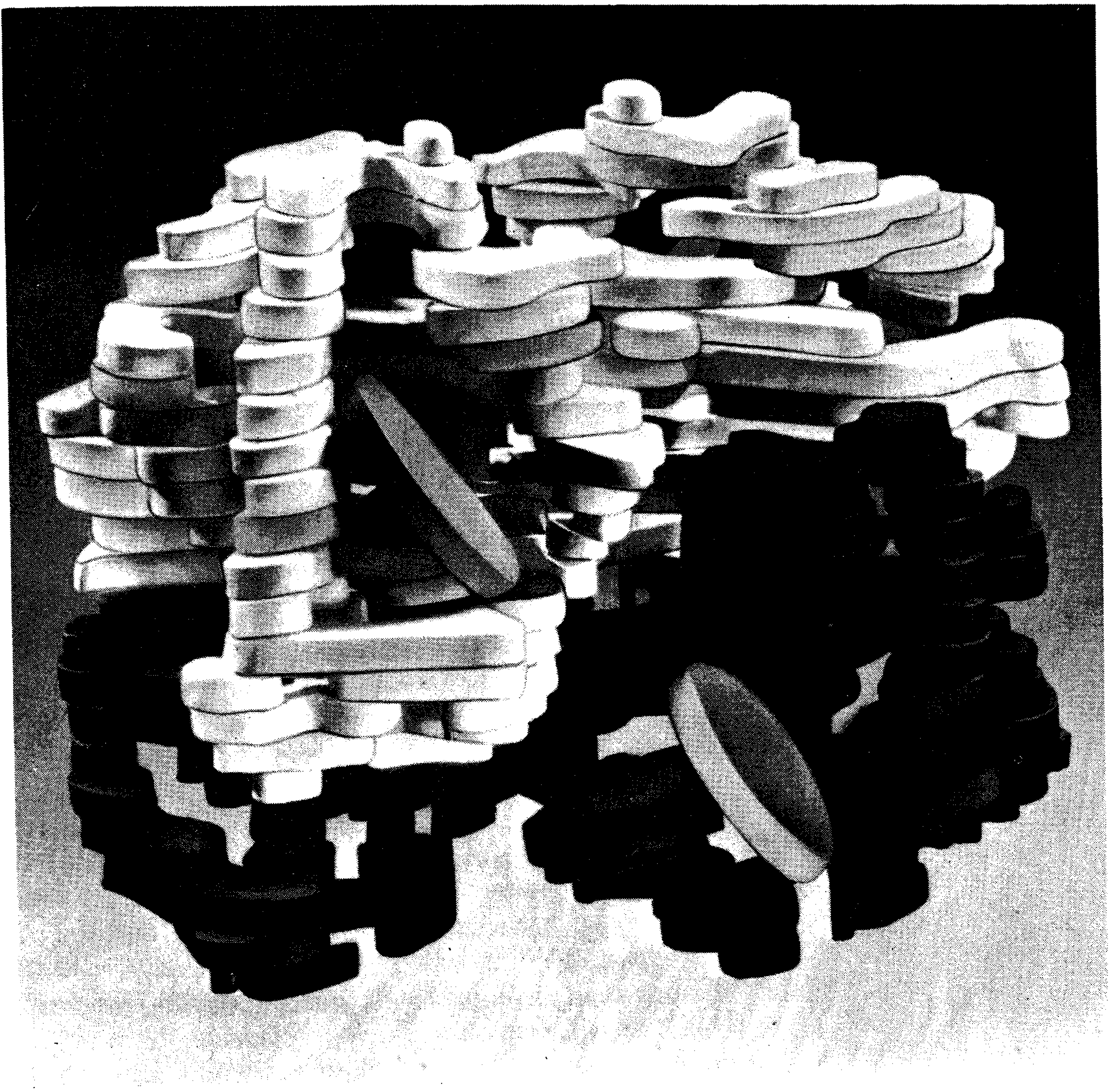
The exceptional crystallographic work of Perutz (who with Kendrew received the Nobel prize for chemistry in 1962) led to a fairly detailed knowledge of the structure of haemoglobin, the essential factor in respiration and the transport of oxygen in the blood. This compound has a molecular weight of approximately 68000, contains about 3000 carbon atoms and four iron atoms and can be broken into two components. These components are a protein (globin) and a rather complex non-proteinaceous co-ordination compound of iron, haem, which is the effective transporter of oxygen (Fig. 103). As the name suggests, globin is a globular protein; it consists of four polypeptide chains, each in turn formed from about 150 amino acids. The tertiary structure of the globin is very complex; it consists of pieces of α-helix separated by regions with different conformations and is constructed in such a way that the haem is enclosed in a specific manner within some pockets of the chain. The folds of the structure depend, although in a way not yet completely understood, on the presence of particular sequences of amino acids. Here, perhaps, are the reasons for the apparent disorder of the primary structure. Because certain biochemical functions take place the macromolecule must possess a tertiary structure which allows the insertion and fixation of reactive centres, for example haem. (In general, the non-protein parts are called *prosthetic groups*.) For this to happen it is necessary that the secondary structure, for example, the α-helix, should be suitably modified in certain positions by the presence of particular amino acids and thus of certain primary structural elements.

The problem is really still more complex. The sequence of amino acids also serves to determine the degree of basic character of the protein, its ability to be solvated by water and to be able to fix the prosthetic groups in a sufficiently stable way and so on. In its turn, the tertiary structure experiences modifications which occur at the prosthetic centre during a reaction. For example, Perutz observed that haemoglobin appreciably changes its shape and expands when the haem contains oxygen. The relationship between the structure and reactivity of haemoglobin and oxyhaemoglobin perhaps represents the path along which an understanding of the secrets of many biological reactions will be reached.

The double helix of DNA

If the structure of a protein is thus closely related to its function, another problem immediately arises. How can proteins be formed with such rigorous precision? What is the chemical mechanism of their synthesis in cells? This investigation is also in its initial stages but what we already know today would have been unimaginable to the researchers of thirty or forty years ago.

It seems certain today that at the base of protein synthesis there is a cybernetic factor. The instructions for carrying out certain reactions are contained in particular molecules which, with a process of positive-negative duplication, can reproduce the information and propagate it to cells by means of suitable carriers. The molecule which possesses the information – the magnetic tape or perforated card – is DNA and the carrier of the message is RNA.



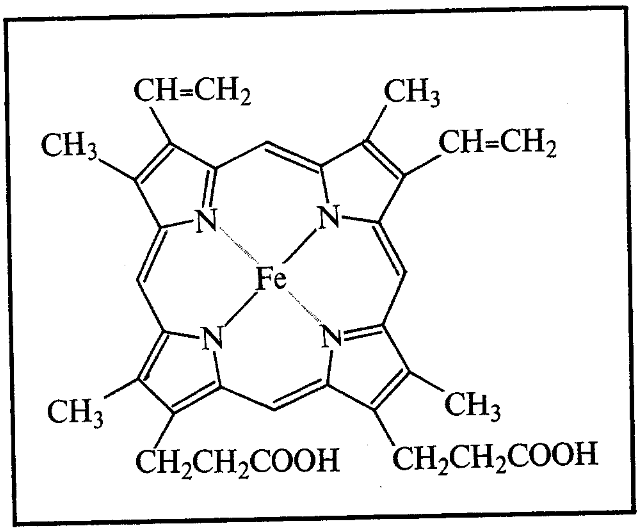


Fig. 103 The structure of haemoglobin as determined by Perutz. The resolution of the detail is not very great but sufficient to identify the shape of the protein chains. On the left, the chemical formula of ***haem***, a molecule containing an atom of iron, is shown. The molecule is fixed in the interior of the protein.

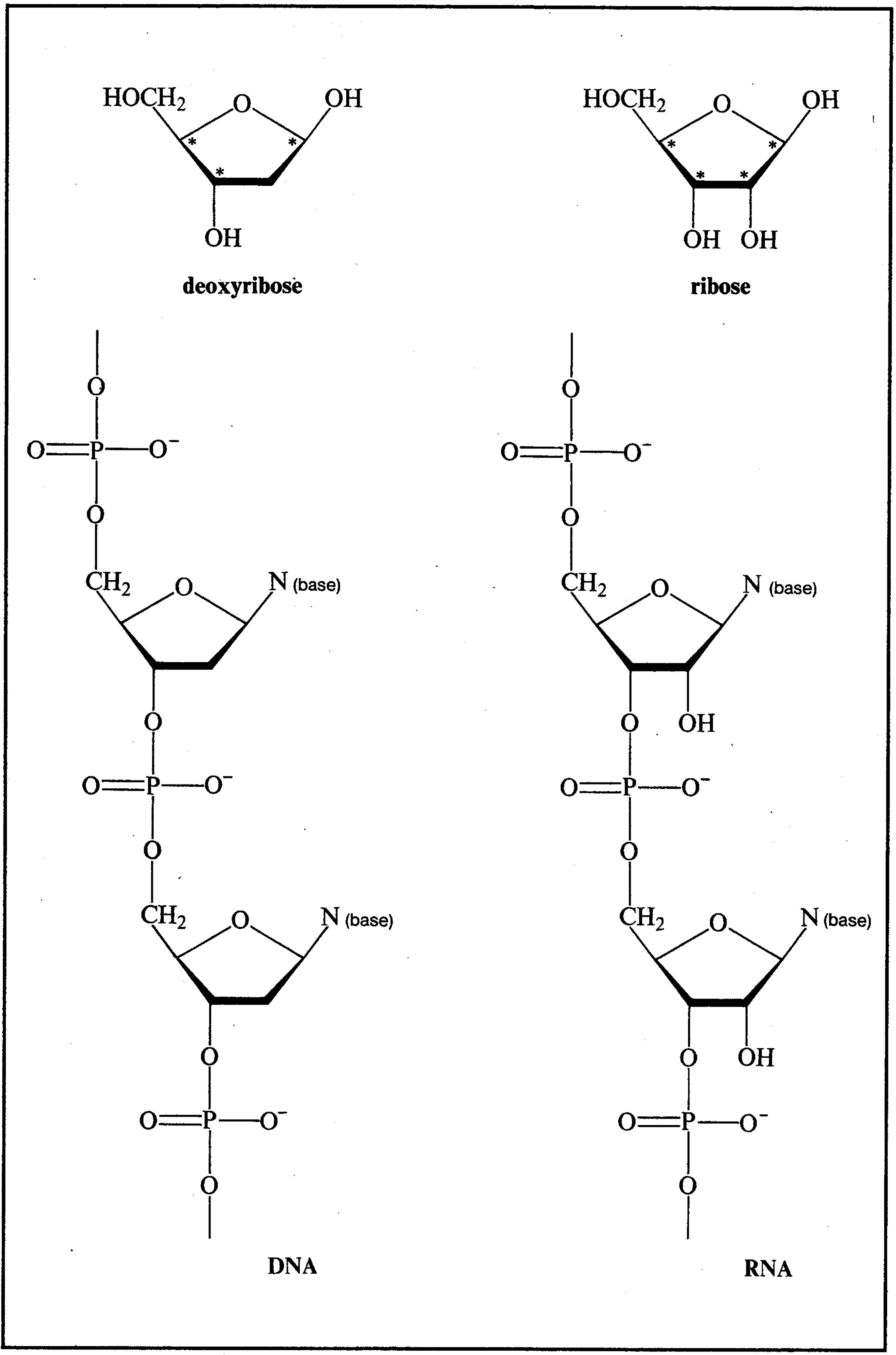


Fig. 104 The formulae of D-deoxyribose and D-ribose. The two sugars are contained in nucleic acids (the asymmetric carbon atoms are indicated with an asterisk). Below, formulae of the chains of the two nucleic acids, DNA and RNA, in the anionic form; they may be considered as alternating copolymers – phosphate-sugar-phosphate-sugar – etc. An aminic base bonded to each sugar residue occupies each position marked N.

DNA are the initials of *deoxyribonucleic acid* and RNA of *ribonucleic acid.* Today we can no longer be satisfied with some initials or a name; we must search for an underlying structure. This is a fundamental difference between the old and the new biochemistry. DNA and RNA are not some magic boxes, where amino acids are introduced and proteins extracted, but very precise compounds with certain structures and functions. Every effort must be made, because the box is no longer magical and it is possible to see inside it. As is usually the case with any new knowledge, there is long and often boring experimental and analytical work to be done. It took many years to understand that DNA is a macromolecule with a very high molecular weight containing, in a 1 : 1 : 1 molar ratio, a phosphoric acid residue, a sugar – deoxyribose – and a mixture of four organic nitrogen compounds, called bases. The fundamental structure can be described as an alternating copolymer – phosphate-sugar-phosphate-sugar-, etc. – in which each sugar residue is bonded to a base (Fig. 104).

The most interesting aspect of this structure lies in the particular nature and distribution of the bases. Firstly, the four bases can be divided into two chemically different classes; the pyrimidines and the purines. Cytosine and thymine (abbreviated by the letters C and T) belong to the first class and adenine and guanine (A and G) to the second. The first base of each pair (cytosine and adenine) is characterized by the presence of an amino group in a certain position while thymine and guanine have a carbonyl group in the same position. On the basis of these data it is already possible to see a certain correspondence between C and G and between T and A. In each pair there is one pyrimidine and one purine ring system, one amino and one carbonyl group (Fig. 105). The results of quantitative analysis give this observation a much greater significance. In the DNA of every living species the complementary bases cytosine and guanine, or thymine and adenine, are present in equal quantity.

Starting from this knowledge and some crystallographic evidence which indicated the presence of a helix, James D. Watson and Francis C. Crick proposed in 1953 the famous double helix model of DNA, subsequently confirmed by the X-ray studies of Maurice H. F. Wilkins. (All three of these scientists received the Nobel prize for medicine in 1962.) We shall try to see more closely what this model consists of and how it interprets with marvellous simplicity the ability of DNA to contain and transmit its information.

We have indicated the qualitative and quantitative correspondence between C and G and between T and A. But when an examination is made of the interactions between the components of each pair the word 'correspondence' can assume a more precise significance. The oxygen and nitrogen atoms of each base are particularly suitable for

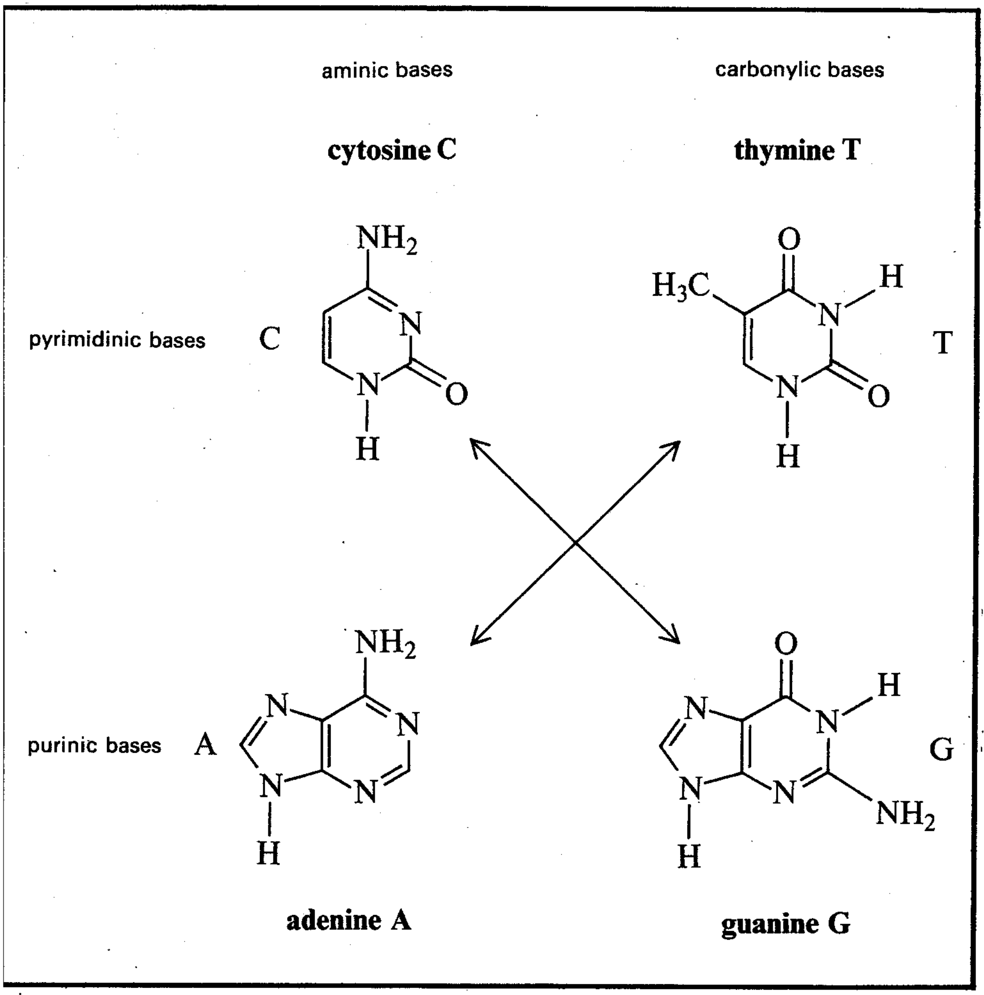


Fig. 105 The four bases of DNA. The arrows indicate the pairs of complementary bases. This relationship, based on quantitative analysis and formal examination of their structures, has an important physical significance.

forming intermolecular hydrogen bonds with their complementary base. Three hydrogen bridges are formed between C and G and two between T and A; if a model of the two pairs is constructed, using the usual interatomic distances and valence angles, a surprising result is obtained: the two pairs have exactly the same dimensions and are perfectly interchangeable with each other (Fig. 106). Consequently, the sugar groups bonded to the two different pairs occupy equivalent positions in terms of distance and relative orientation. One may then consider that the two polymeric chains are rigidly connected through the hydrogen bridges of the bases, as the two shafts of a ladder are connected by the rungs. The presence of an asymmetric sugar like 2-deoxyribose (strictly 2-deoxyribofuranose since it exists in a five-membered cyclic form derived from furan) imposes a clockwise helical arrangement on the polymeric chain. This is valid for both chains which can thus be represented as a spiral staircase wound round an imaginary pole (Fig. 107).

Crystallographic examination has fully confirmed the validity of this picture and has provided many other new facts: depending on the exact form, DNA has 9 or 11 steps for each complete revolution, 0·34 nm high, and often inclined with respect to the axis of the chain.

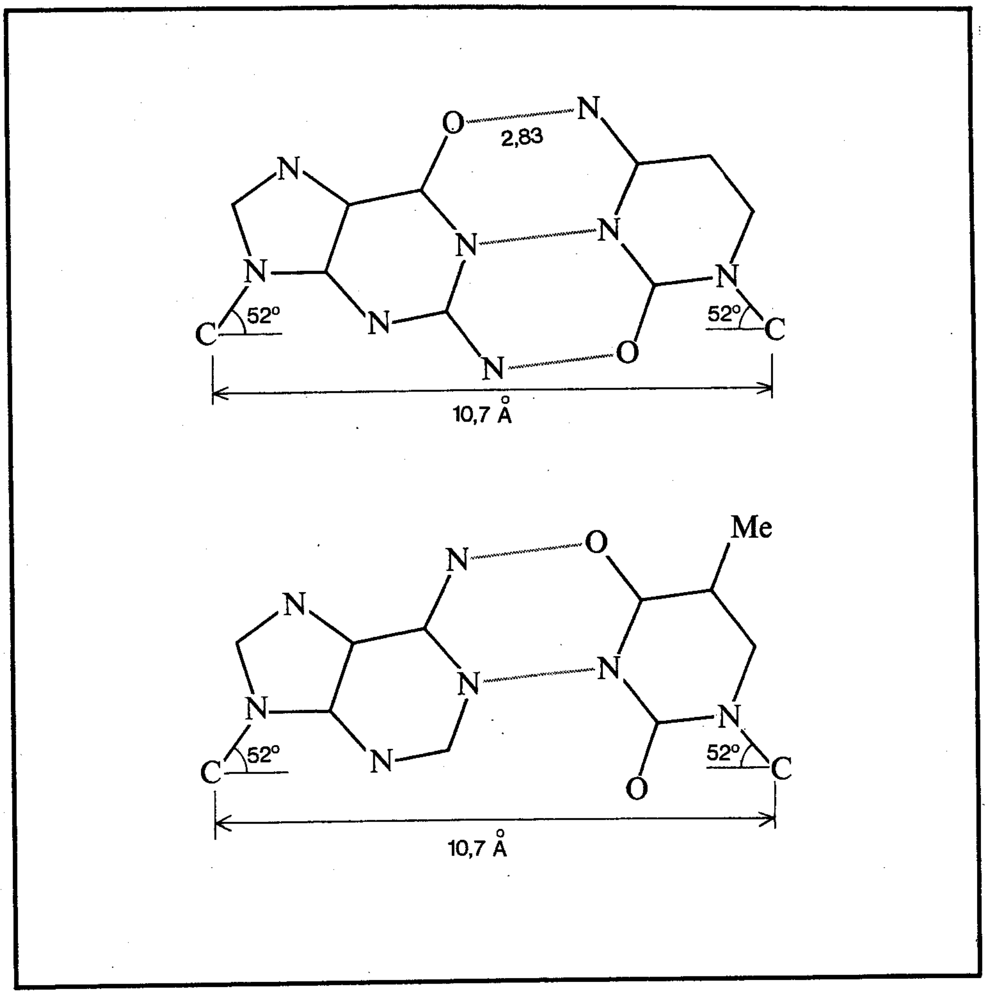


Fig. 106 The complementary nature of the bases can be explained by supposing that the chains are associated in pairs and that the base-pairs G-C and A-T are joined by hydrogen bonds. The two pairs of bases thus connected occupy the same space and are even interchangeable without altering the separation and orientation of the two chains to which they belong.

Additionally, and this is of great importance, it has been shown that DNA chemically isolated and thus 'killed' (in the sense of having been separated from the cells) has the same structure as 'living' DNA, i.e., that present within the living cell.

Duplication of DNA and the code for protein synthesis

From Watson and Crick's model, it is clear that the two chains complement each other. For a hypothetical sequence of bases in a chain (for example, . . . ATGCACTG . . .) there is a corresponding sequence in the other (. . . TACGTGAC . . .). The two chains can be considered as prints of each other or, if we use photographic language, they are in a positive-negative relationship. The chemical and structural characteristics of DNA allow us to explain some of its biological properties in a rather simple way.

Firstly, DNA is a molecule capable of reproducing itself within the cell. The particular feature of this reproduction is that it occurs in a very exact manner. An error would have incalculable consequences since it could alter the inherent information contained in

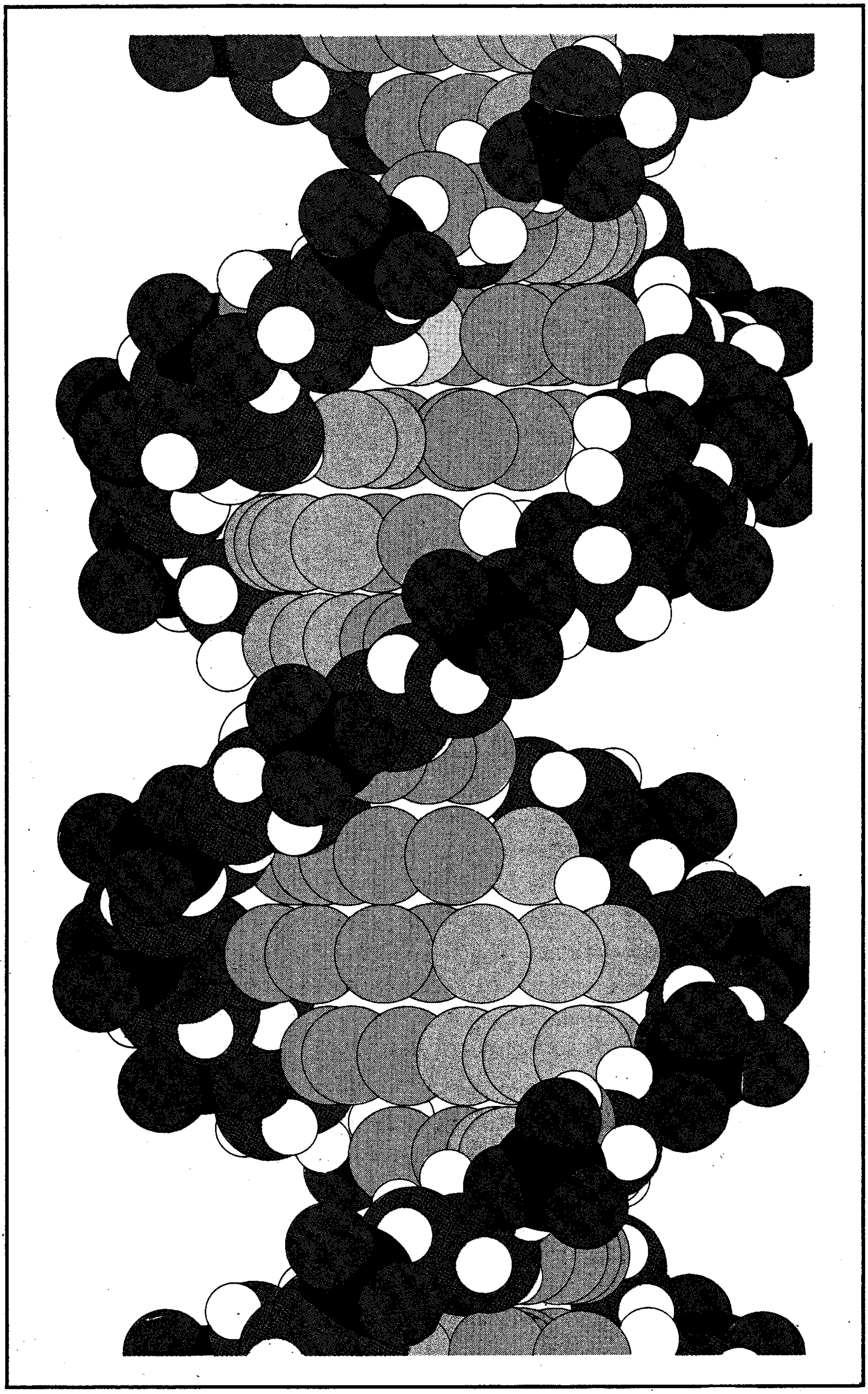


Fig. 107 The double helix of DNA determined by means of crystallographic analysis.

the molecule. (It seems, in fact, that certain genetic mutations may arise from some chemical changes of this type.) The correspondence between the two chains offers us a simple and rational explanation of this reproduction. In the act of duplication (replication) and under the action of particular enzymes which open the hydrogen bonds, the double chain separates into two branches, positive and negative, and both are reactive. In a way similar to a photographic contact process, each of these reproduces on itself an exactly complementary chain to which it is connected by hydrogen bonds and with which it rewinds into a double helix. Thus, from one double chain, two are obtained at the end of the process and, successively, four, eight and so on (Fig. 108). The very high specificity of the A-T and C-G relationship ensures that structural mutations do not occur even after a very large number of replications.

Having explained the mechanism of replication or, at least, provided a very probable and reasonable hypothesis for it, the problem changes to the significance of the arrangement of the bases, to the genetic inheritance of DNA and its utilization. DNA contains the instructions which regulate the sythesis of proteins coded in an alphabet of four letters, A, T, C, and G. The problem is now to find the words which govern the synthesis, taking into account that there must be at least 20, as many as there are amino acids. A simple calculation shows that the words with two letters (AG, CA, CG, etc.) are not sufficient for the purpose since there are only sixteen such words (i.e., 4×4). At least three-letter words are necessary, although these provide more 'words' than required ($4 \times 4 \times 4 = 64$). Some redundancy, or the fact that several words may have the same significance (in chemical terms, that one or more triplet bases may be associated with the same amino acid), is certainly not an absurd possibility. Moreover, words might have a different significance if they concerned not only the primary structure but also the secondary and tertiary. The hypothesis that the code for the synthesis of proteins consists of three-letter words (i.e., triplets of bases) has been confirmed by a series of experiments in which genetic mutations are introduced and the corresponding base sequences then chemically determined. This research was initiated about ten years ago by Nirenberg and recently concluded with the excellent synthetic work of Gobind Khorana. (Recently, both were awarded the Nobel prize for medicine.)

At this point, however, it is necessary to introduce another of the elements which relates DNA to the proteins. This is RNA. In the biological field, the necessity of postulating this intermediate arises because DNA is present only within the cell nucleus while protein synthesis occurs principally outside it in the cytoplasm. Ribonucleic acid, present both in the nucleus and the cytoplasm, consists

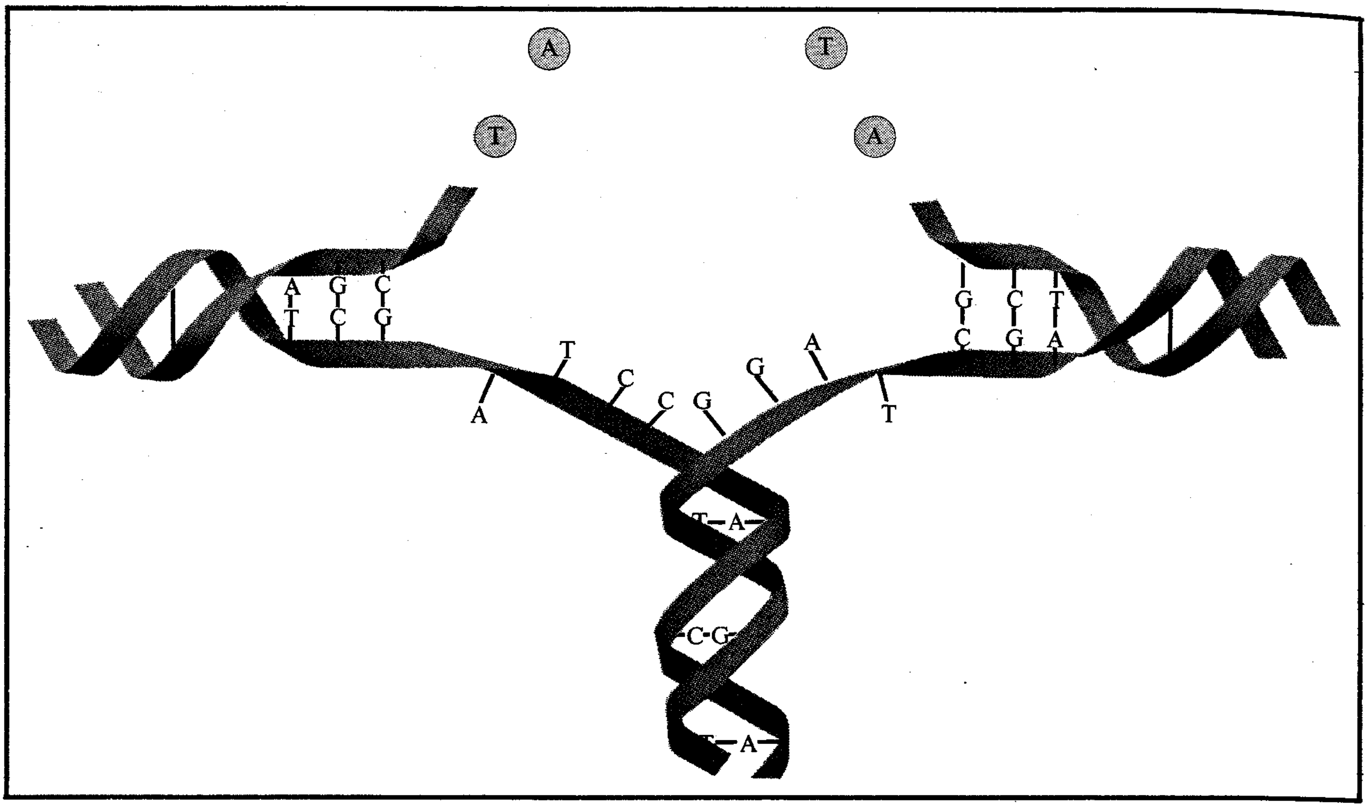


Fig. 108 The formal scheme for the duplication of DNA. The double helix opens and a complementary chain, exactly identical with the initial one, is reproduced on each matrix.

of an alternating copolymer – sugar-phosphate-sugar-phospate – analogous to DNA but with ribose instead of deoxyribose as the sugar residue (thus it contains an extra hydroxyl group). In RNA as in DNA the four bases are complementary to each other in two pairs; but the pairs are cytosine-guanine (C-G) and uracil-adenine (U-A), and not thymine-adenine (T-A) as in DNA (in addition other bases are present in small quantities). The difference between uracil and thymine is quite small (uracil lacks a methyl substituent) and does not alter the structure of the double helix. The molecular conformation of RNA appears to be very similar to that of one of the crystalline forms of DNA.

More exactly, we must speak of at least three types of RNA: messenger RNA, ribosome RNA and soluble, or transfer, RNA. The first is formed by negative copying from DNA by the process described earlier for the replication of DNA and carries the 'message' after translation into a new script (ACGU rather than ACGT), outside the cell nucleus; the second, closely bonded to the ribosomes, carries out the protein syntheses; the third, with the lowest molecular weight, has the ability to bond itself to different amino acids and to place them in the way required by the instructions received.

Table VI. The code for protein synthesis*

U U U	PHE	C U U	LEU	A U U	ILEU	G U U	VAL
U U C	PHE	C U C	LEU	A U C	ILEU	G U C	VAL
U U A	LEU	C U A	LEU	A U A	ILEU	G U A	VAL
U U G	LEU	C U G	LEU	A U G*	MET	G U G*	VAL
U C U	SER	C C U	PRO	A C U	THR	G C U	ALA
U C C	SER	C C C	PRO	A C C	THR	G C C	ALA
U C A	SER	C C A	PRO	A C A	THR	G C A	ALA
U C G	SER	C C G	PRO	A C G	THR	G C G	ALA
U A U	TYR	C A U	HIS	A A U	ASN	G A U	ASP
U A C	TYR	C A C	HIS	A A C	ASN	G A C	ASP
U A A	C. T.	C A A	GLN	A A A	LYS	G A A	GLU
U A G	C. T.	C A G	GLN	A A G	LYS	G A G	GLU
U G U	CYS	C G U	ARG	A G U	SER	G G U	GLY
U G C	CYS	C G C	ARG	A G C	SER	G G C	GLY
U G A	?	C G A	ARG	A G A	ARG	G G A	GLY
U G G	TRY	C G G	ARG	A G G	ARG	G G G	GLY

* A definite amino acid corresponds to each triplet of bases. The significance of only one triplet is still unknown at this moment. 'C. T.' signifies chain termination. The two triplets marked with an asterisk signify also the beginning of the chain.

The last twenty years of research on the nucleic acids and on the synthesis of proteins have shown gigantic progress, culminating in the synthesis of DNA molecules with predetermined codes, although we are still in the initial stages of obtaining biochemical knowledge of elementary life processes. We know that there is a code with a well-defined chemical significance and we also know how to read it but we still know very little about the detailed structure of the different molecules or of the effective functioning of these processes.

Macromolecular biochemistry in its various aspects and problems represents without doubt the most fascinating field of research for the modern student of the life sciences.

VIII

Structure and behaviour of chemical compounds

The ability to predict the properties and behaviour of a compound represents the first step towards the realization of a chemistry by 'engineering', the 'designing' of compounds in the same way that an automobile or a building is designed. Perhaps the day is not far away when it will be possible to speak of molecules made to measure for some predetermined requirement. In many simple cases it is now possible to do this but not always by the logical application of first principles. Much of the knowledge we possess in the field of pharmacology or concerning the physical properties of materials comes more from an examination and systematic comparison of different behaviour than from the application of previously determined rules. Today we have many correlations between the properties and structure of entire classes of compounds but it is almost always knowledge limited to a certain area with no general validity. The effort required to reach a deeper knowledge of phenomena is immense and much of what we have said in the previous chapters concerning conformational analysis, chemical reactivity and natural and synthetic macromolecules relates to this line of modern chemical research.

However, the problem can be tackled at different levels, particularly with respect to the different types of behaviour. The methods of instrumental analysis, for example, show even the smallest changes in structure. An infrared or nuclear magnetic resonance spectrum represents a 'fingerprint' of the individual molecule; it will be different from that of another, only slightly different, compound. In the more favourable cases the structure of the compound can even be completely calculated directly from the spectra. In the next pages we would like to discuss some macroscopic properties, certain aspects of the chemical and physical behaviour which can be perceived without the use of complicated equipment.

A further elaboration should first be made of the relationship between stereochemistry and the properties of matter. Generally, phenomena are considered stereochemical only if they are related to the difference in behaviour of stereoisomers, that is to say those compounds which, owing to a different arrangement of their atoms in space, are uniquely different from each other. In the course of this book, however, we have considerably extended the significance of the word stereochemical. Any molecule, even one with the simplest structure, is a stereochemical phenomenon since the atoms of which it is composed, independently of whether or not there are other possible stereoisomers, have a definite arrangement in space. In a broad sense, therefore, one can describe as stereochemical any relationship between the structure of a compound and its chemical and physical properties. Expressed in these terms such a statement is open to an obvious criticism: any structure is determined also by a certain distribution of electrons among atoms and thus it should be possible to derive all the aspects of behaviour equally well from electronic factors, such as the electronegativity of the atoms, the polarization of the bonds and so on. It is therefore necessary to distinguish, or to try to distinguish, truly stereochemical factors from electronic factors, which are also peculiar to each type of structure, and from the effects of functional groups, etc.

In this regard it can be affirmed that where conditions of symmetry, crowding, shape, rigidity or mobility of molecules are involved, it is possible to speak of stereochemical factors, without considering – we repeat – the existence or non-existence of other isomers. This does not mean that stereochemical factors may not be particularly significant in determining the differences in the behaviour of stereoisomers themselves, for example, those of optical antipodes.

In the course of this chapter we shall try to describe some examples of the incidence of stereochemical factors, understood in the sense just described.

The fusion of molecular crystals

A melting point is defined as the temperature at which a crystalline phase changes to an amorphous phase, generally a liquid. For example, the melting point of pure ice is 0°C at atmospheric pressure. More exactly, the melting point is determined by the relationship between the enthalpy (or heat) of fusion and the variation of entropy that accompanies this process ($Tf=\Delta Hf/\Delta Sf$). The value of the melting point depends on many factors, not all of which can be easily explained in a qualitative treatment since it is an inter- rather than an intramolecular property; moreover, the value of the energy involved in the fusion process is generally very small and thus easily influenced by secondary factors. (We refer here to molecular

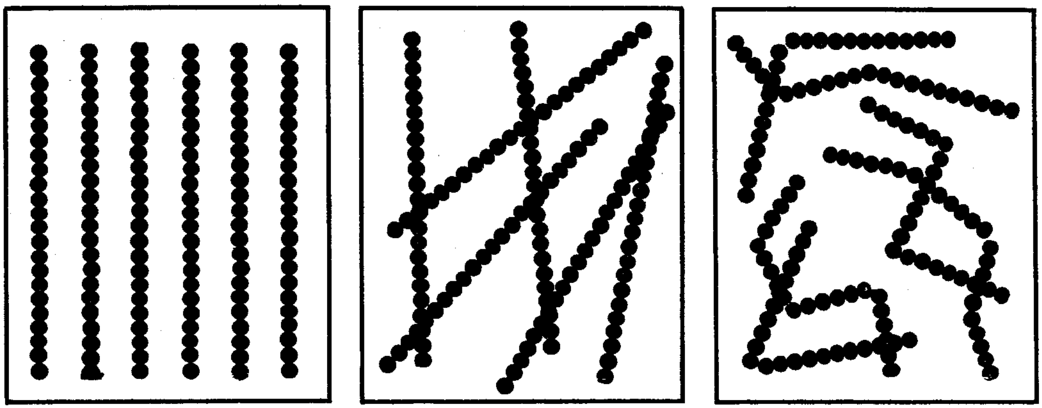


Fig. 109 **The two stages in which the process of fusion ideally takes place. One can assume that the molecules in the crystal are first arranged in a regular manner; they then separate and change their mutual orientation while still remaining rigid. Finally, they assume various shapes according to statistical laws.**

crystals where the molecules maintain their own individuality and are bonded to each other through very weak forces, Van der Waals forces.)

In the examination of fusion there are two states to be taken into consideration, the crystalline and the liquid. In a series of similar compounds, the greater the energy difference between the two states the higher will be – to a first approximation – the melting point. The stability of the crystal lattice of non-polar compounds (for example, the hydrocarbons) can be roughly correlated with the ability of the molecules to occupy the available space in the best possible way, without leaving holes and without necessitating strong deformations and internal tensions in the molecular structure. This is favoured by a regular external shape and is strongly influenced by the type of symmetry possessed by the molecule.

The fusion process can be considered as the breaking of the Van der Waals attractive forces between different molecules, which then separate and assume a random orientation. Van der Waals forces also act in the liquid state but, because of the disorder between the molecules, their total strength is lower than in the solid state. If the molecules are flexible, i.e., can exist in more than one conformation, they are distributed in the liquid state between the different conformations according to statistical laws. The greater disorder thus introduced increases the entropy of the liquid phase which is thus more stable than an analogous system formed from rigid molecules (Fig. 109).

Symmetry and the mobility (or rigidity) of the molecules are two of the most important factors which regulate the fusion process. Within certain limits it is possible to predict that the melting point will be particularly high for very symmetrical and rigid molecules. As an example, we cite the case of adamantane, a hydrocarbon with a formula $C_{10}H_{16}$, completely rigid and of the highest symmetry (group T_d), for which the melting point is about 270°C. By comparison we recall that *n*-decane ($C_{10}H_{22}$), which has a very mobile structure, melts at −30°C and that naphthalene ($C_{10}H_8$), very rigid but less symmetrical, melts at 80°C (Table VII).

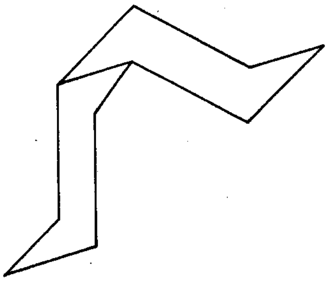
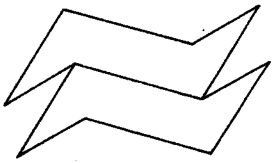
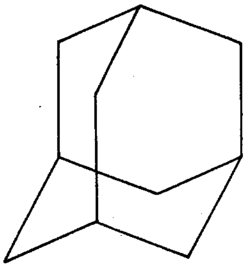
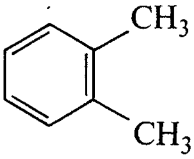
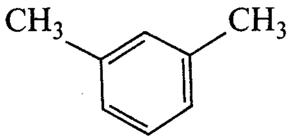
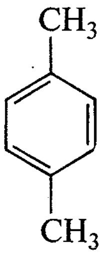
The melting point represents a parameter of some importance for the characterization of compounds with a low molecular weight. (Solubility is also associated with melting-point: a high-melting substance is generally not very soluble.) But it acquires particular importance in macromolecular chemistry. We have seen how it determines the elastic properties of a rubber and how, to obtain a textile fibre of good quality, a rather high melting point is required, above that of boiling water and, if possible, also above that of a normal clothes-iron. Polypropylene (m.p. 176°C) and Nylon 66 (264°C) have numerous advantages from this point of view over other widely used fibres which shrink in washing and melt if accidentally ironed.

In recent years a large research effort has been made to produce polymers resistant to high temperatures. This effort has been supported by the space race and the alluring research contracts of NASA. The conditions for life in spaceships and especially in interplanetary space are extremely arduous. The variation of temperature on the lunar surface between day and night is about 400°C and extremely high temperatures are also reached inside a space capsule during re-entry into the atmosphere. Because of this it is necessary to find new materials having good mechanical flexibility together with high melting point and decomposition temperature. The approach most followed and so far most profitable in this field was suggested by considerations of the type given above. The great majority of polymers resistant to high temperature consist of very rigid chains formed from a succession of rings and in some cases from multiple chains (the so-called ladder polymers) such as those shown in Fig. 110.

Turning to a more stereochemical example, it seems interesting to examine the behaviour of enantiomorphous compounds and their mixtures in the fusion processes. The phenomenon of temperature itself contains nothing concerning dissymmetry. (On the contrary, it is associated with the idea of disorder and thus of statistical compensation between mirror-image phenomena.) It is thus impossible to see how the melting-point of the D optical antipode can be different from that of the L. Enantiomorphous compounds therefore have the same melting point. The destruction of a D crystal and the formation of a D liquid phase bears a perfect mirror-image relationship with (and is thus isoenergetic with) that of the L antipode.

This is not generally true for the fusion of a racemic compound,

Table VII. Relationship between molecular structure and melting point

	$C_{10}H_{18}$ ***cis*-decalin**	−43°C
	$C_{10}H_{18}$ ***trans*-decalin**	−30°C
	$C_{10}H_{16}$ **adamantane**	+268°C
	C_8H_{10} ***ortho*-xylene**	−25°C
	C_8H_{10} ***meta*-xylene**	−47°C
	C_8H_{10} ***para*-xylene**	+13°C

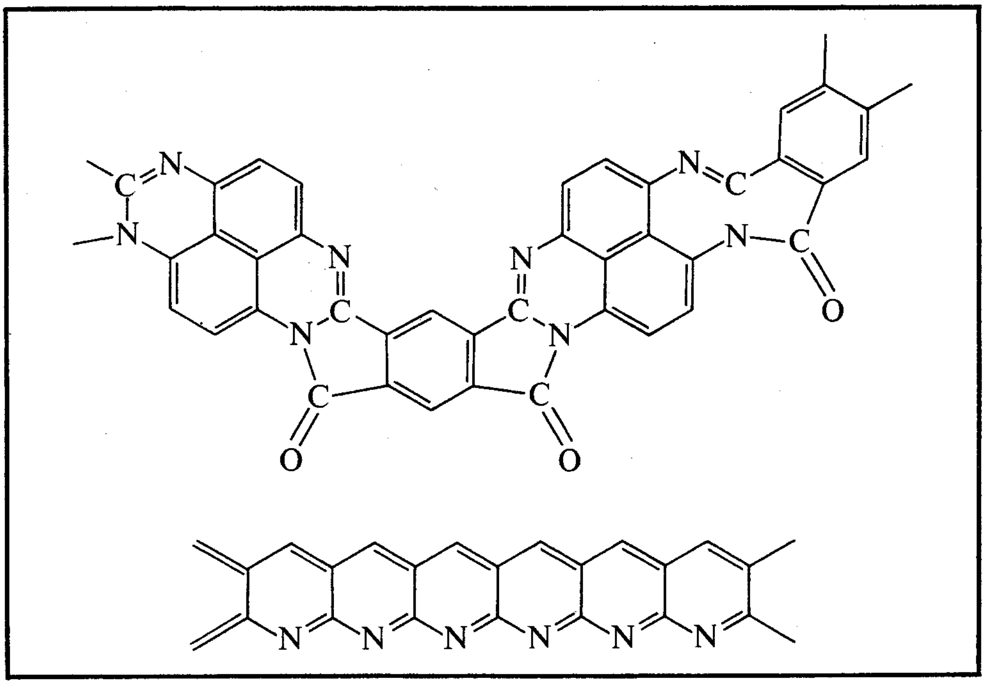


Fig. 110 Two polymers resistant to high temperatures. The first is obtained by polycondensation of a tetra-amine with a tetracarboxylic acid; the second by cyclization and aromatization of a ready-formed polyacrylonitrile polymer. Both have a rigid polycyclic structure. Their melting points are well above 400°C.

i.e., one which contains equal quantities of D and L molecules (Fig. 111). It is convenient to distinguish here between three different cases, depending on the shape and symmetry of the molecules and crystals. It can happen, for example, that D and L have a practically identical shape and that one molecule can replace the other in the crystal lattice. In this case, mixtures of D and L in whatever ratio have the same crystalline form and a melting point identical with, or very near to, that of the pure components; these are called mixed crystals. If, instead, D and L have a shape notably different from each other, it is necessary to examine separately the case in which the D-L aggregate is more or less stable than the D-D (or L-L) aggregate. In the first case the simultaneous presence of D and L in the same crystal cell imposes the existence of crystallographic symmetry elements of a reflective type, i.e., a centre or planes of symmetry (two molecules with the same sign can only be related to each other by a rotation or translation axis). Different combinations of symmetry elements imply different space groups and thus different types of crystals. One can then understand why an aggregate consisting of D and L molecules in equal quantities must crystallize in a different way from the pure optical antipode and have a different (lower or higher) melting point. In other words a *racemate* (a crystal containing both D and L molecules) represents a particular diastereoisomer different from DD and LL.

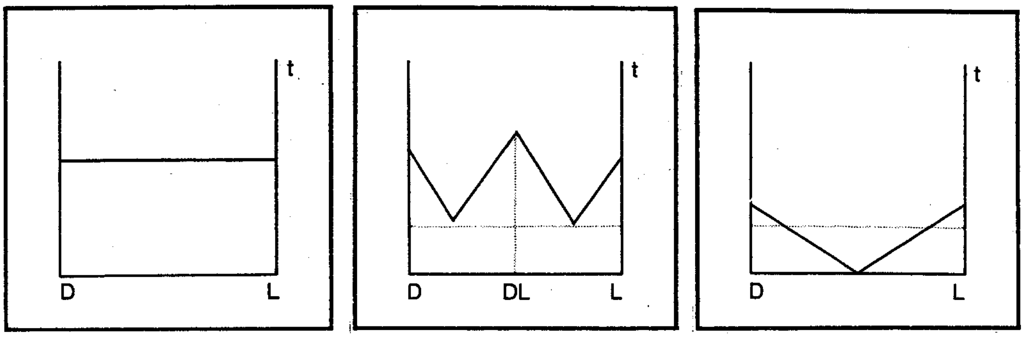


Fig. 111 **Fusion diagrams of optical antipode mixtures. On the left, the melting point is practically constant over the whole range of compositions (mixed crystals are formed); in the centre, the formation of a racemate whose crystals are formed from an equal number of dextro and laevo molecules; on the right, the formation of a low-melting eutectic mixture.**

When, on the other hand, a hypothetical crystal DL is less stable than a mixture of DD and LL crystals, a racemate is not formed but instead a *eutectic* phase, with a lower melting point, and containing minute crystals of both enantiomorphs. It may be asked why the eutectic has a lower melting point than the optical antipodes, given that all the crystals are of the pure DD and LL type. From the start we have said that in the fusion processes it is necessary to consider the liquid state as much as the crystalline. The fusion of a single DD crystal will thus be quite different if the liquid phase consists of both D and L molecules rather than all D molecules. Because of the configurational disorder in the former case, the liquid phase is more stable than previously (since there is an increase of entropy for the disordered mixture of the D and L forms) and, consequently, the melting point is lower.

The action of drugs

The property of diastereoisomerism is also required for an explanation of the biological and pharmacological properties of optical stereoisomers. This field may appear to have little in common with the foregoing discussion about the melting of optically active substances. But the description of the melting point behaviour has helped to outline the notion that diastereoisomerism is not confined to intramolecular interactions but also plays a part in intermolecular processes. Moreover, it must not be forgotten that the crystalline state represents the most highly organized and ordered aspect of non-biological matter and, as such, presents many analogies with the most complex systems in living organisms.

One of the fundamental considerations for the comprehension of biological phenomena is the following: living matter consists, for the greater part, of dissymmetric molecules and of the two possible optical antipodes only one is present. It can be deduced from this that many biochemical reactions are strongly influenced by stereochemical factors and, in particular, that different behaviour will be shown by two optical antipodes towards a given reagent. To illustrate this point better, some analogies may be useful. A perfectly ambidextrous person would not have any difficulty in throwing a ball with either the right or the left hand. A ball is not a dissymmetric object but is highly symmetrical and its relationship with the right hand is the same as that with the left. But when two people face each other, the fact that the ball is thrown with the right or the left is not without relevance. One may have seen the discomfort experienced by a tennis player, fencer or boxer when meeting a left-handed adversary. His attacking and defensive plans are totally altered because the situation he must face is different from the one to which he is accustomed. This is a rather trivial example of diastereoisomerism. With the more usual analogy of the hand and the glove, we can also introduce a quantitative observation. The more specific and exclusive is the relationship between the hand and the glove, the tighter and closer-fitting is the glove. Thus there is nothing abnormal in the apparent paradoxes, for example, that *dextro*-asparagine or *dextro*-glucose taste sweet but the *laevo* antipodes do not. The human organism is a very dissymmetric structure and with all probability, at the molecular level, so are the ends of the taste-buds. Furthermore, the *laevo* antipodes would be sweet for a man who was our enantiomorph, made from D amino acids and L sugars, coming from a hypothetical planet on which life bears a mirror-image relationship to that on earth.

Where the differences in behaviour between optical antipodes is large and of practical utility is in the action of drugs. Many active pharmacological substances have one or more asymmetric atoms and can thus exist in different stereoisomeric forms. A very important problem in therapy and industrial production is to ascertain which stereoisomer has the greater activity and whether the others have a negative, neutral or positive action. The consequences are evident: if one of the optical antipodes has a decidedly negative action its elimination from the pharmaceutical preparation is essential. This operation is generally quite difficult and costly.

The influence of the steric configuration on pharmacological properties is clearly visible in the case of chloramphenicol, the well known antibiotic (Fig. 112). Chloramphenicol contains two asymmetric carbon atoms and there are thus four stereoisomeric forms, grouped in two pairs of optical antipodes called, respectively, *erythro* and *threo*. (These are the two general names which can be used to distinguish between diastereoisomers containing two asymmetric carbon

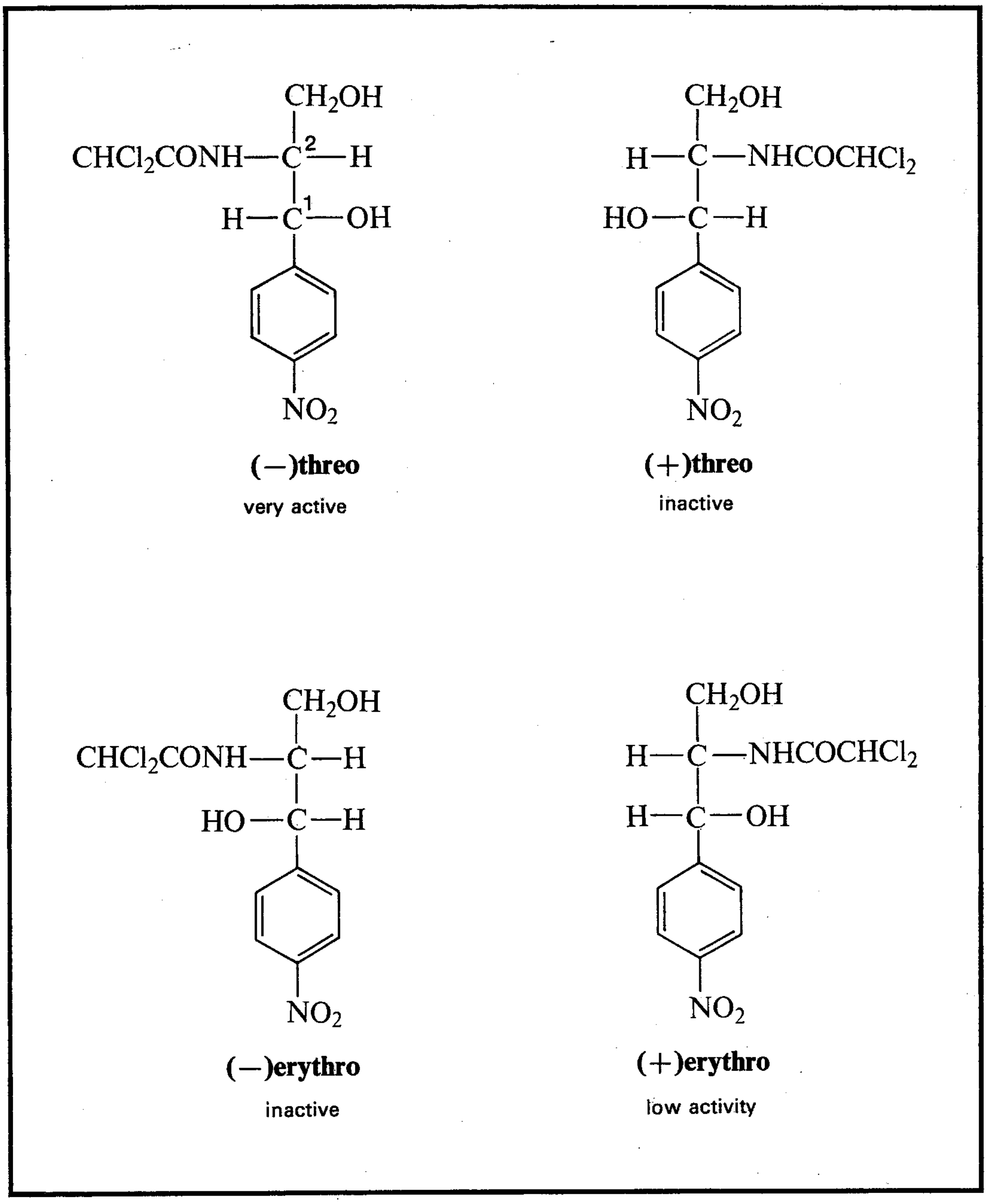


Fig. 112 Only one of the four stereoisomers of chloramphenicol is pharmacologically very active; another has a much reduced action and two are inactive. The two active compounds have the same configuration around asymmetric atom 1 but have the opposite sign of rotation.

atoms.) Of the four isomers, the (—)-*threo* is a powerful antibacterial agent; a certain bacteriostatic action is also shown by (+)-*erythro* but (+)-*threo* and (—)-erythro are totally inert. Two observations can immediately be made. The first is the marked difference in behaviour between the optical antipodes in (+)-*threo*-(—)-*threo* and (+)-*erythro*-(—)-*erythro*; the second is the presence of positive effects in two different stereoisomers. Structural investigation shows that the (—)-threo and (+)-erythro configurations are the same at one of the two asymmetric carbon atoms, indicated in the formulae with the number 1. One can deduce from this that the arrangement around this atom has a more important function than that around the second. The inversion of configuration of atom 1 totally nullifies the pharmacological action while inversion of atom 2 reduces it between 50 and 100 times but does not destroy it altogether. In passing, it is interesting to note that the sign of optical activity in the chloramphenicol isomers depends principally on the configuration at atom 2.

A tentative explanation of the pharmacological behaviour of optical stereoisomers is the theory of the *three points*. This is a very successful theory, even though it is frequently criticised. The three point theory is based on the argument that the two optically antipodal molecules resting on a surface at three points (like a table with at least three legs) produce different arrangements. In the case of a single asymmetric carbon atom the three points of contact are formed by the three substituents X, Y and Z which have a clockwise sense in the one instance and an anticlockwise sense in the other. Using the hypothesis that the receptor is also asymmetric and presents a succession of complementary points X′, Y′ and Z′, complete superposition is possible in the one case while in the other the contact occurs only on two of the points considered (Fig. 113). On the experimental plane this hypothesis is supported by the fact that the molecules of drugs are often polyfunctional, i.e., they contain more than one atom or group of atoms susceptible to reaction or co-ordination with suitable atoms or groups of the receptor. Moreover, a triple co-ordination rigidly fixes one molecule to the other while a contact in two points, or in only one, allows vibrational or rotational movements that render the selectivity of the relationship less efficacious. This forms an acceptable hypothesis for the mode of action of drugs. But the theory of three points loses its value when its significance is unduly extended by considering it, on little evidence, to be a fundamental rule of biochemical behaviour and stereochemical behaviour in general.

Logically, the only general rule is based on the symmetry of compounds and their relationships. If these relationships are identical or antipodal (i.e., if they are different only in the vector and not the scalar sense) the connected processes are isoenergetic; if they are different in the numerical sense, leading to diastereoisomerism, the energies of the ground and transition states are different and thus the chemical behaviour is different. This is obviously a purely theoretical discussion and says nothing about how the phenomena of diastereoisomerism will reveal themselves in practice. Symmetry arguments only tell us that the right hand is suitable for the right-hand glove in a different way from the left hand; we must obtain experimental verification by observing how the fingers insert themselves in a precise way, without losing movement and yet without having too much play. Only at this level, as a particular hypothesis

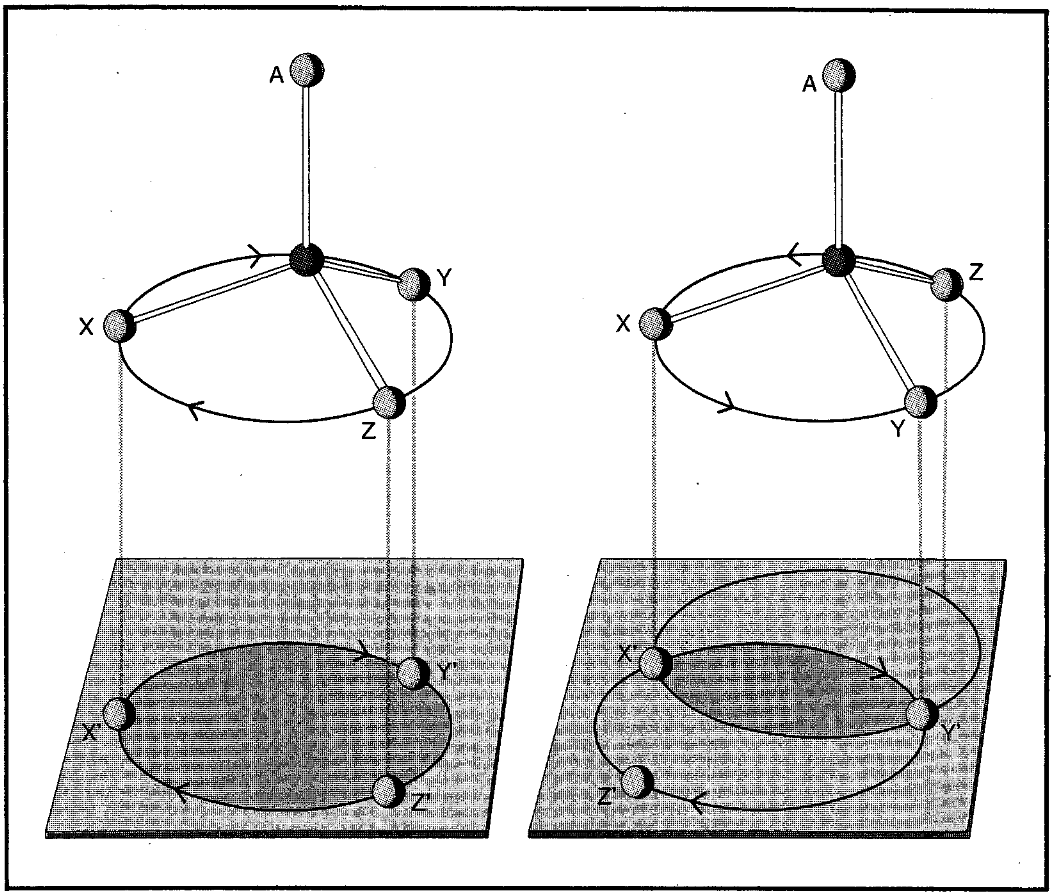


Fig. 113 The theory of the three points predicts that only one of the two optical antipodes will combine with an asymmetric receptor (on the left). The other optical antipode will have at the most only two points of contact.

susceptible to verification and proof, can the theory of the three points be maintained and also show itself to be very useful.

Another quite useful picture for explaining the relationships between receptor and drug is that of the lock and the key. The maximum biological action occurs when the drug molecule has a shape suitable for the structure of the receptor centre. The argument here does not rest on two or three points but on a general arrangement of the two reagents in such a way that their interaction is the most favourable. If this picture is true (and there are no valid reasons for denying it), if the receptor and drug are in a complementary relationship, we have an experimental instrument for investigating the structure of biologically active centres. A systematic examination of the pharmacological properties of compounds with progressively diverse structures allows us to identify the essential characteristics of the receptor structure. A study of this type was made for a series of natural analgesics (like morphine) and for synthetic ones. From the relationship which exists between analgesic reactivity and molecular shape, a plausible hypothesis was formulated for the structure of the receptor centre sensitive to these drugs. In turn, from the knowledge of these structural elements, it has been possible to suggest new molecules likely to be endowed with strong analgesic power.

Enzymatic reactions

A large part of this discussion about drugs can be extended to other aspects of biological chemistry and in particular to the action of enzymes. These are the catalysts of the reactions in living organisms, often having a very much greater activity than normal catalysts used in synthetic chemistry. This fact is easily appreciated. In laboratory or industrial practice, the choice of reaction conditions is quite free and a slow process can be accelerated by increasing the temperature, the pressure and the concentration of reagents or by changing the

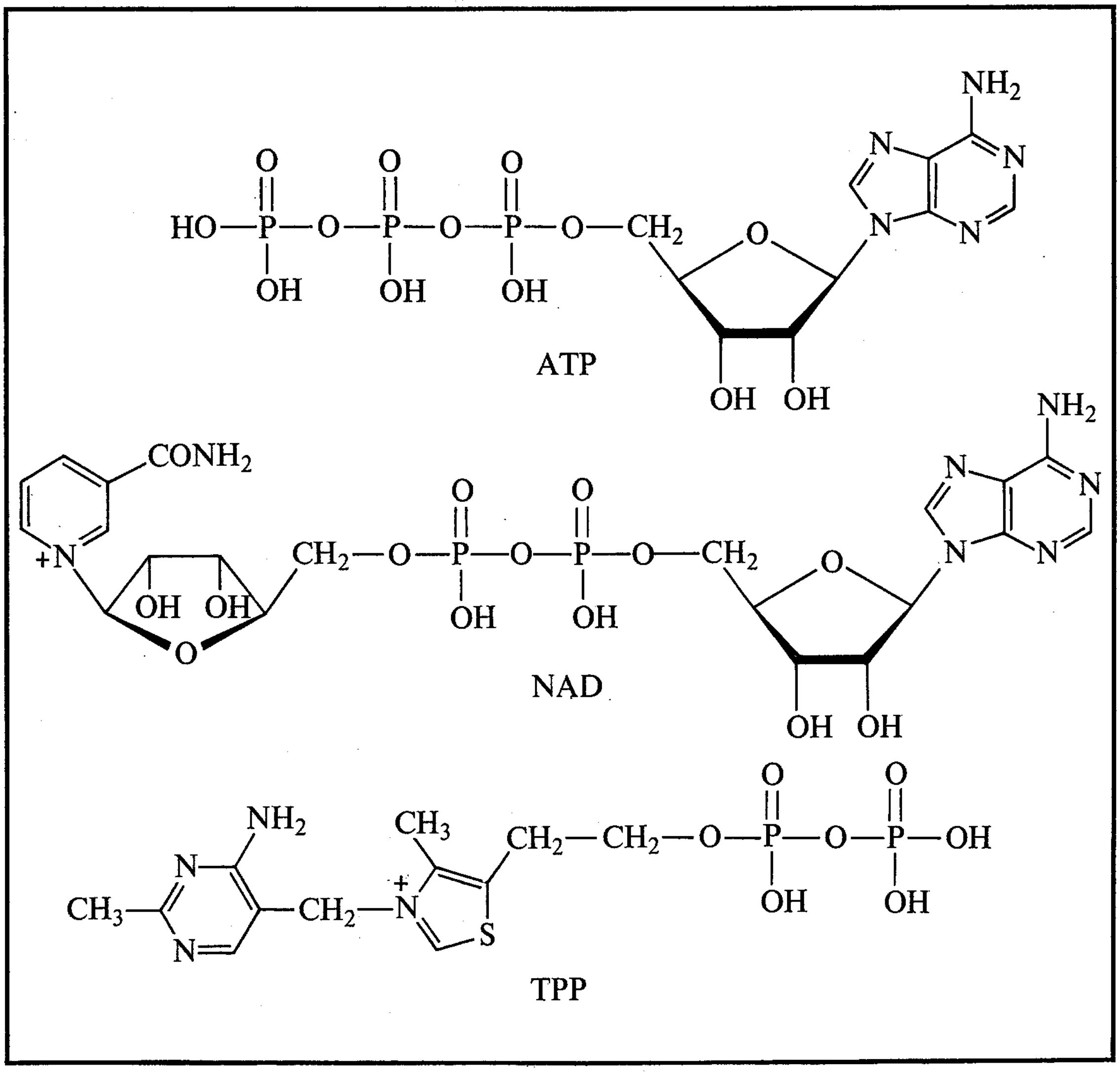


Fig. 114 Formulae for some of the most important co-enzymes. From the top, adenosine triphosphate (ATP), nicotinamide-adenine dinucleotide (NAD) and thymine pyrophosphate (TPP).

solvent. But in living organisms the chemical reactions must take place within well defined limits, at 37°C or even less, in aqueous solution with a practically fixed pH, at atmospheric pressures and frequently at very low concentrations. It is thus logical that in its evolutionary process nature has developed extremely efficient catalysts to ensure the rapid and orderly completion of the chemical reactions of life.

The principle on which the action of enzymes is based consists in the lowering of the activation energy for the reactions which occur under their influence, a lowering which is greater the more complex are the immediate surroundings of the reactive centre. The lowering of the activation energy leads, other things being equal, to an increased rate of reaction. (A lowering of 1 Kcal per mole corresponds to a five-fold increase in the rate of a reaction taking place at room temperature.) The influence of the complexity of a molecular system can be observed by examining the influence of iron catalysts on the decomposition of hydrogen peroxide. The activity increases millions of times if, instead of using simple ferric ions obtained by dissolving a ferric salt in water, *catalase* is used, an enzyme containing a co-ordination compound of iron (a ferroporphorin similar to the haem of haemoglobin) bonded to a protein.

In chemical terms the enzymes consist of proteic molecules (*apoenzymes*) combined with other non-proteic molecules called *co-enzymes*. The intermediate state of an enzymatic reaction is formulated as a complex between the enzyme, the co-enzyme and the substrate (the molecule which is to react). The reaction occurs in reality between the co-enzyme and the substrate but the presence of the enzyme favours the development of the reaction by lowering the energy content of the transition state through the formation of weak bonds with the reagents.

The co-enzymes are often *nucleotides,* consisting of a sugar, a phosphate group and one or more bases, similar to those found in the chain of the nucleic acids. Co-enzymes are known by their initials. ATP signifies adenosine triphosphate, ADP adenosine diphosphate and NAD nicotinamide-adenine dinucleotide (nicotinamide is the vitamin PP or anti-pellagra factor) (Fig. 114). Even when they do not have a nucleotidic structure, the co-enzymes generally contain phosphate groups as in TPP (thiamine pyrophosphate), a phosphorylated derivative of vitamin B_1. In the light of knowledge of the structure of co-enzymes it has become possible to understand some fundamental points of biochemical reactions, such as the importance of phosphorus and some of its derivatives, and the rôle of some vitamins.

The study of enzymes is also of technological interest. The food and pharmaceutical industries make considerable use of the enzymatic processes of fermentation. It is enough to think of alcoholic fermentation to imagine the enormous economic importance of these processes. In this field, even greater developments are expected in the not too distant future. One of the problems which afflicts humanity is the scarcity of protein. Beyond the great exploitation of other natural resources (such as those of the sea), one of the predicted solutions lies in the enzymatic production of amino acids and proteins for animal food at low cost starting from oil, ammonia and air. Some processes have already reached the pilot-plant stage, and the composition of these synthetic products is very similar to that of natural proteins.

Many enzymes and co-enzymes are produced today in the crystalline state and in high purity. With their help it is possible to reproduce in vitro, i.e., in the absence of living cells, many of the reactions which occur in life. Moreover, it is possible to carry out many reactions on non-biological substrates, notably widening our view of the action of enzymic chemistry. The fundamental characteristic of these reactions is their selectivity. There are different enzymes for different reactions (oxidations, reductions, hydrolysis, decarboxylations, etc.) and often the enzymes are capable of distinguishing between one substrate and another, even if the substrates are chemically similar. For example, some hydrolytic enzymes which regulate the digestive process of the proteins – pepsin and chymotrypsin – have a specific action at the centre of the peptide chain and are specific for the splitting of the amide bond between a definite pair of amino acids.

The fact that enzymes are made from protein – they are asymmetric molecules – also explains their stereoselectivity. As already noted, Pasteur was able to bring about selective enzymic reactions on one optical antipode while leaving the other unaltered. It is this selectivity, among others, which allows the extremely high optical purity of living organisms. A D amino acid or an L sugar is expelled by the living organism or is rapidly destroyed and thus does not become a disturbing element in biological macromolecular structures. In other cases, the selectivity does not concern the optical antipodes but diastereoisomers. Maltase, for example, is a specific enzyme for the α-glucosidic bonds of starch but does not touch the bonds of cellulose. On the other hand emulsin easily hydrolyses cellulose but leaves starch unaffected.

Out of the many examples of enzymic syntheses, we choose only one from amongst the more significant at the stereochemical level, one which is highly instructive with regard to the mechanism of these reactions (Fig. 115). The enzyme alcoholic dehydrogenase catalyses the reaction between the co-enzyme nicotinamide-adenine dinucleotide (which in its oxidized state is most exactly represented

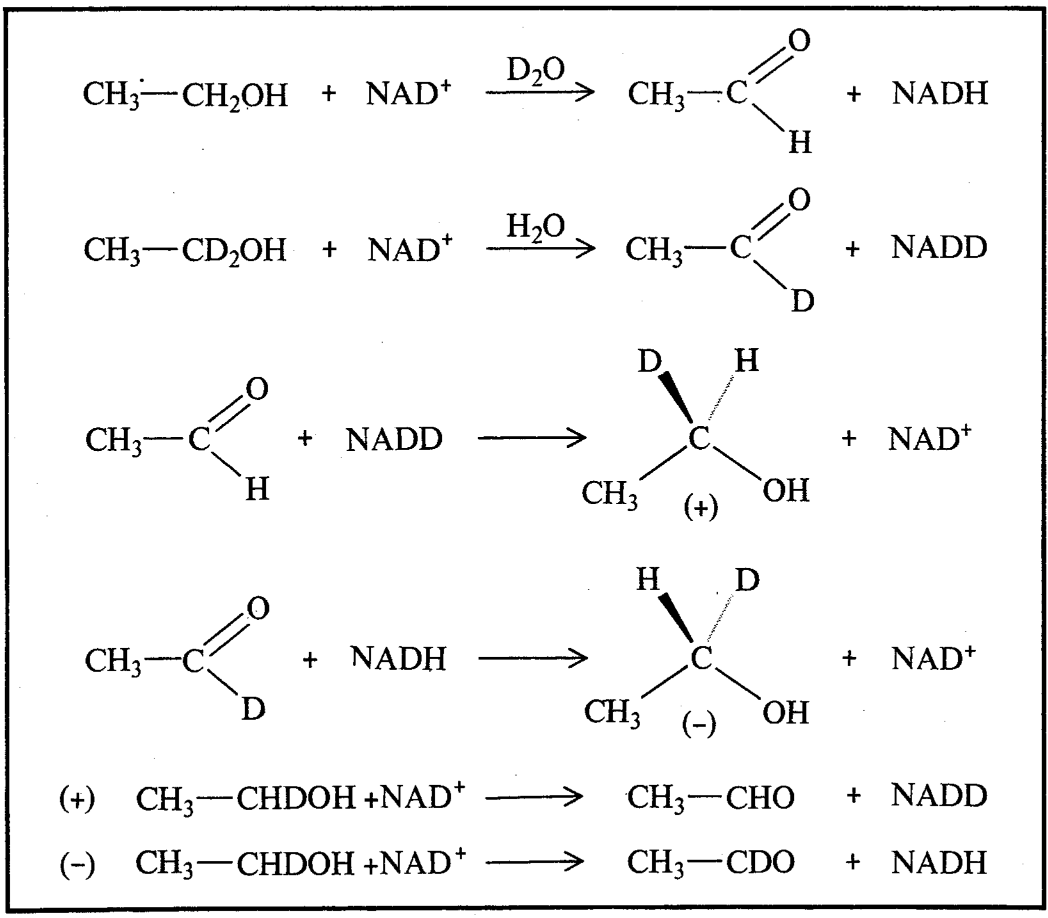


Fig. 115 Some stereochemical aspects of enzymatic reactions are clearly illustrated in the oxidation reductions carried out by Westheimer on ethyl alcohol. (1) Oxidation of the alcohol in heavy water: no deuterium is incorporated. (2) Oxidation of the deuterated alcohol: deuterated aldehyde and deuterated reduced co-enzyme are produced. (3) Reduction of the non-deuterated aldehyde with the deuterated co-enzyme (+) monodeuterated alcohol is obtained. (4) Reduction of the deuterated aldehyde with the non-deuterated co-enzyme: (−) monodeuterated alcohol is obtained. (5) Oxidation of (+) deuterated alcohol: non-deuterated aldehyde is obtained. (6) Oxidation of the (−) deuterated alcohol: deuterated aldehyde is obtained. The co-enzyme reacts in a completely stereospecific way, transferring or removing an atom of hydrogen (or deuterium) always at the same position.

as NAD^+) and ethyl alcohol to give the reduced form of the enzyme (NADH) and acetaldehyde. If this reaction is carried out in heavy water, D_2O★, neither the reduced co-enzyme nor the acetaldehyde contains deuterium. This result demonstrates that the solvent, water,

★ Heavy water, D_2O, is a molecular species in which the two hydrogen atoms normally with mass 1 are substituted by heavy hydrogen atoms with mass 2, also called deuterium atoms and symbolized by the letter D. Even though the chemical reactivity of heavy water is substantially equal to that of normal water, many physical properties are different, particularly those of a spectroscopic nature. The differences are reflected, in a more or less marked way, in other deuterated molecules in which one or more hydrogen atoms are substituted by deuterium and they permit a definite identification of the quantity and position of these atoms. The techniques of isotopic labelling are among the most efficacious methods existing today for investigating chemical structures and mechanisms.

does not participate in the reaction. On the other hand, if the co-enzyme is made to react, in normal water, with ethyl alcohol deuterated in position 1, the reduced deuterated co-enzyme (which we shall call NADD) is obtained along with deuterated acetaldehyde. The deuterated co-enzyme NADD can be used to reduce non-deuterated acetaldehyde (these reactions are all easily reversible). The ethyl alcohol thus obtained is deuterated and optically active, with the sign (+). (In spite of the small difference between hydrogen and deuterium, a carbon atom substituent of the type C_{ABHD} is really asymmetric and in favourable cases like this the molecular dissymmetry gives rise to a measurable optical activity.) If the deuterated acetaldehyde first obtained is reduced with non-deuterated NADH, the resulting ethyl alcohol is again found to be deuterated and optically active but with a negative optical activity. If the two optically antipodal deuterated alcohols (+) and (−) are dehydrogenated with the co-enzyme NAD^+, then from the positive antipode normal acetaldehyde is obtained and from the negative, deuterated acetaldehyde.

This exceptional stereochemical cycle, carried out by F. M. Westheimer some years ago, is only superficially surprising and constitutes one of the most rigorous examples of chemical logic. What are the conclusions to be drawn from it? Inversion of the order of introduction of the isotopes (first hydrogen, then deuterium or *vice versa*) leads to an opposite result. As there is no equilibration, this demonstrates that the process is controlled kinetically and not thermodynamically . The phenomenon is identical with that already described in chapter V in connexion with asymmetric syntheses, but with the notable difference that here the stereospecificity is complete and has been obtained by making only negligible modifications in the reagents (deuterium in place of hydrogen). The experiments just described show in a very clear way that the two hydrogen atoms of the methylene group of ethyl alcohol are not equivalent and that the enzyme-co-enzyme system is definitely capable of distinguishing between them. One only of the atoms is transferred from the substrate to the co-enzyme or *vice versa.* The formal explanation of these phenomena, which for many years represented a real puzzle even for the specialists, is really quite simple. The phenomenon is one of prochirality or potential asymmetry about which we have already spoken in chapter V. The two hydrogen atoms of ethyl alcohol and the two faces of the acetaldehyde molecule are not identical but mirror images of each other; the asymmetric enzyme-co-enzyme system chooses from the two possibilities the reaction path with the lower activation energy. The marking of a particular position with a deuterium atom does not alter the mechanism but makes evident an otherwise unobservable effect.

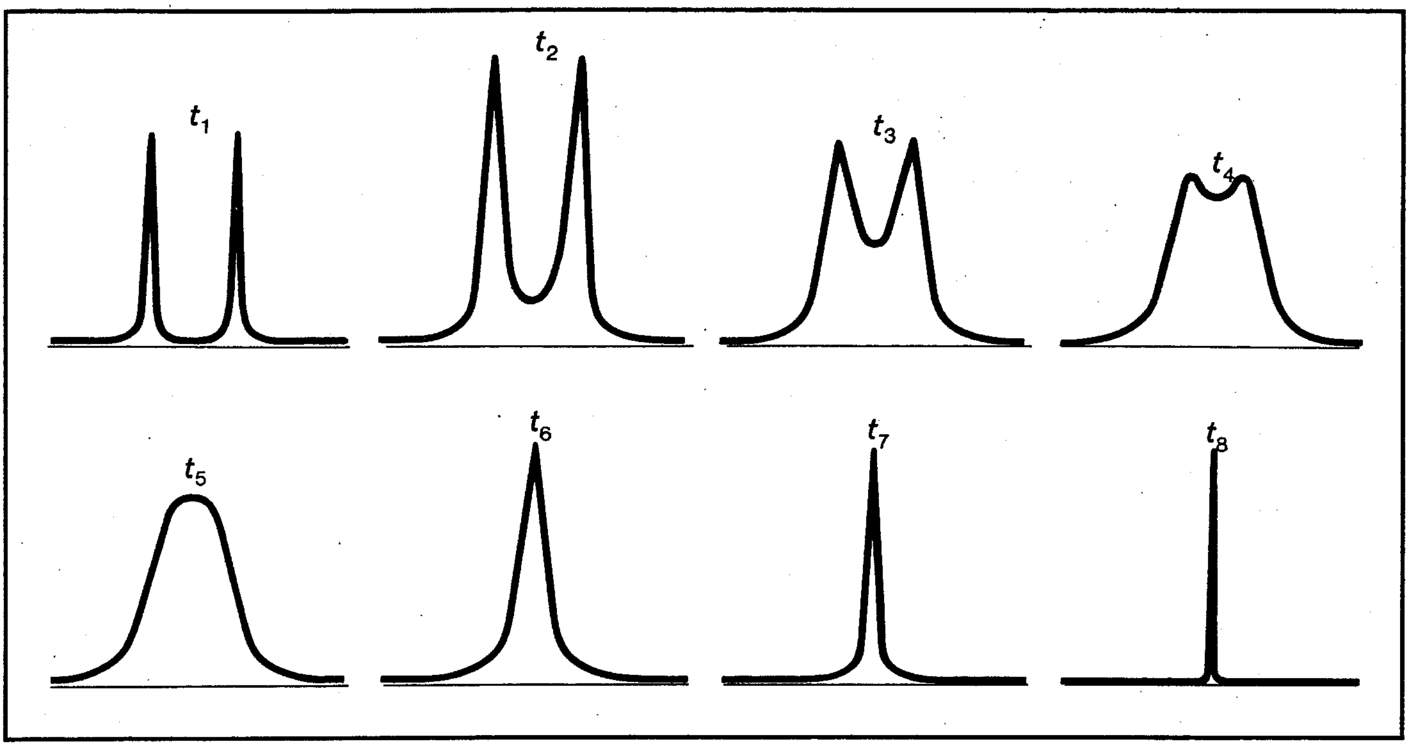


Fig. 116 **The temperature variation of the nuclear magnetic resonance spectrum of deuterated cyclohexane, $C_6D_{11}H$. The point at which the two resonance signals become smeared-out is called the coalescence temperature.**

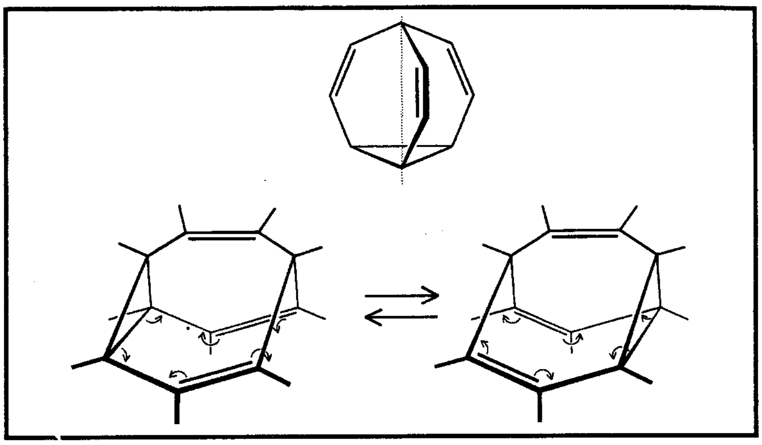
Fluxional molecules

Earlier, in a discussion of the structure of cyclohexane, we said that the results of the various experimental techniques, symbolized by a camera with variable shutter speeds, are different and depend on the time of observation of which each particular technique of investigation is capable. A molecule may thus sometimes be observed instantaneously (to a first approximation) but at other times it will appear 'blurred' and we shall observe the time average of the forms which the molecule successively assumes.

Interest in the study of non-rigid molecular structures arose principally from the increased use of the techniques of nuclear magnetic resonance (nmr). This is a form of spectroscopy which is very sensitive to the spatial arrangement of the atomic nuclei and is characterized by an observation time suitable for showing the type of time-dependent phenomena discussed above. Previously these had been completely ignored. There are two particular indications of the presence of molecular transformations of the type just mentioned: the nmr spectra are simpler than expected and there is a change in the spectra with temperature. We have already seen that the rate of a chemical reaction depends on temperature, but this is not the only molecular phenomenon which is temperature-dependent. In the present case the rates of the processes under examination vary with temperature and thus changes in temperature lead to radical changes in the observed spectra. At low temperatures, where the transformations are slower, an 'instantaneous' spectrum may be observed or, sometimes, the sum of the spectra of two or more molecular species (in cases where more than one species has an average lifetime sufficiently long to be observed individually). At higher temperatures, however, the spectrum is simpler and the spectral parameters relating to each atom have values intermediate between those which the single atom would have if it were observed instantaneously before and after the transformation.

A fairly simple example of a molecular transformation in which the initial and final states are identical is the chair-chair interconversion of cyclohexane. The rate of this transformation is such that only a single line is observed in the nuclear magnetic resonance spectrum at room temperature. During the transformation the hydrogen atoms which were initially equatorial become axial and *vice versa* (see Fig. 37, p. 184). Figure 116 shows the spectrum of cyclohexane containing eleven deuterium atoms and one hydrogen, $C_6D_{11}H$. (This is preferred to the usual cyclohexane because of the greater simplicity of its spectrum.) On lowering the temperature the line is first seen to broaden and then to split into two lines. At a still lower temperature the two bands move further apart and become sharper. They correspond to the resonance frequencies of the

Fig. 117 The molecular formula of bullvalene. During the movement of the electrons indicated by the arrows (one electron corresponds to each arrow) a molecule is transformed into another identical with the first and so on.



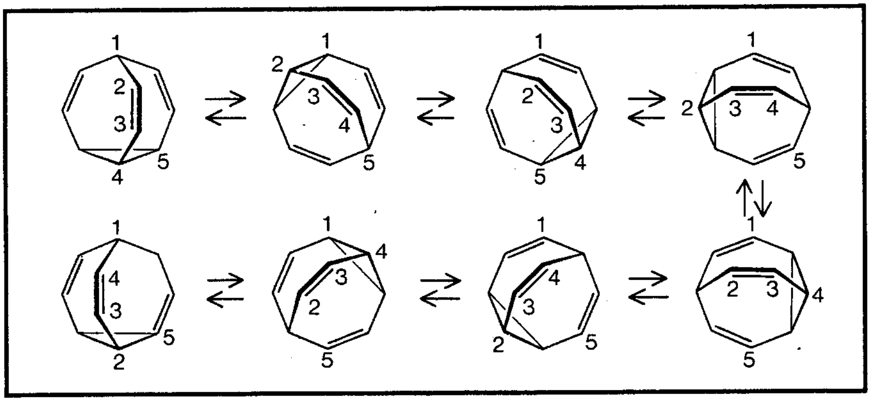


Fig. 118 This series of reactions shows how the carbon atoms in bullvalene do not maintain their positions with time. The sequence 1, 2, 3, 4, 5 is changed after a few steps to 1, 4, 3, 2, 5.

equatorial and axial hydrogens and have equal intensity, in agreement with the fact that the two conformers have an equal probability of existence.

Phenomena of this type sometimes have a conformational origin in the sense that they are caused by variation in the angles of rotation around the bonds. However, they may also arise from other causes, such as the processes of exchange of atoms between different molecules or within the same molecule, or by very large deformations of the valence angles. The most notable example is provided by bullvalene.

In 1962 von Doering brought to the attention of scientists a hypothetical molecular structure which should have exceptional properties. It was of an unsaturated, polycyclic hydrocarbon with the formula $C_{10}H_{10}$, to which he gave the name bullvalene (Fig. 117). In the following year the compound was obtained by synthesis and it displayed exactly the predicted characteristics. Bullvalene possesses threefold symmetry and it is possible to recognize four differing groups of hydrogen atoms. These are: the hydrogen atom at the apex, two groups of hydrogen atoms bonded to unsaturated carbon atoms (each group consists of three atoms), and, finally three hydrogens bonded to the cyclopropane ring. At room temperature the nuclear magnetic resonance spectrum is quite confused. (It is near the point of coalescence.) But at higher temperatures it shows a single line only, as though the hydrogen atoms were of a single type.

To explain this fact it is necessary to assume that the molecule undergoes rapid internal rearrangements in which one of the σ bonds of the cyclopropane ring is broken and the electrons from that bond participate in the formation of the two π bonds. At the same time two π bonds are broken and the electrons participate in the formation of a σ bond. A new cyclopropane ring different from the first is formed. Consequently the hydrogen atoms continually change their electronic environment, leading to complete dynamic equivalence. But on close examination of this system, a unique feature is noticed. The atoms (both of hydrogen and of carbon) do not have a stable position of equilibrium, but migrate throughout the whole molecule. Carbon atoms which are close in one instant are far apart in the next; this can be seen by following the reaction path indicated in Fig. 118.

It is advisable to point out that, in spite of a superficial resemblance, there is no real relationship between the behaviour of bullvalene and that of benzene (see chapter II). In benzene there is a phenomenon of delocalization of the electrons in a uniform way over the whole ring, such that the symmetry of the 'instantaneous' structure is hexagonal (group $\mathbf{D}_{6h}$). The method of writing two formulae with alternating double bonds in different positions is a purely artificial representation (see Fig. 24, p. 58). In bullvalene successive reactions really occur and the equivalence of the atoms occurs over (relatively) long terms. Moreover, a simultaneous equivalence of ten atoms (of the carbons or hydrogens which are present) is, for geometrical reasons, impossible. By symmetry, in fact, the ten atoms would have to be arranged on the surface of a sphere in equivalent positions; this is an impossibility. It is geometrically possible to have 4, 6, 8, 12 or 20 equivalent points on a sphere but not 10.

Molecules like bullvalene are called fluxional molecules and belong to the larger class of non-rigid molecules. Other examples of this behaviour are known in inorganic and organometallic chemistry where the phenomenon is very widespread and allows investigation in depth of the nature of the chemical bond and of the pathways of many reactions.

The chemical process of vision

To conclude this brief and fragmentary exposition of the relationship between compounds and their properties it seems very appropriate to consider a phenomenon in which the reader is participating at this moment. The fact that one can read these lines, the characters of the print and the figures in this book, has a stereochemical explanation.

The basis of the phenomenon of vision is a well defined chemical reaction, a *cis-trans* isomerization, an essentially stereochemical reaction.

The human eye is sensitive to electromagnetic vibrations with a wave-length between 400 and 700 nm, a very narrow interval with respect to the entire electromagnetic spectrum which extends from radio waves (hundreds of metres long) to X-rays and to γ-rays whose wave-lengths are much less than 0·1 nm. On the other hand, the range of sensitivity of the eye is extremely large with respect to intensity: the ratio of the intensity of light scarcely visible from a star and that of the full midday sun is one to a thousand million. Such great adaptability is obtained by the use of two different types of photosensitive elements, cones (for intense light) and rods (for the weak light). The latter, very numerous and sensitive, possess a substance called rodopsin as an active element. When light strikes the eye the rodopsin changes colour through a chemical reaction and is then slowly regenerated. For this reason, nocturnal glares are dangerous and the eye requires quite a long period of adaptation to again accustom itself to scotopic vision, that is, vision with little light.

Rodopsin consists of a protein, scotopsin, and a prosthetic group, retinene; the latter is a highly unsaturated aldehyde with a structure very similar to that of vitamin A (Fig. 119). With its very unsaturated structure (containing 5 C═C double bonds and one C═O), retinene is easily excited by a luminous impulse. We recall that the energy necessary to excite a molecule photochemically diminishes with an increase in the number of double bonds and that the energy of radiation is inversely proportional to its wave-length. The chemical structure of retinene therefore strictly determines the position of the visible range of the spectrum. A simpler compound, providing it were active and ignoring other complications (such as the transparency of the lens), would push the visible zone towards what we call the ultraviolet whilst one with a still longer unsaturated system would push it towards the infrared.

Of the numerous geometrical stereoisomers of retinene, only the *trans-cis-trans-trans, neo*-retinene, can be bonded with scotopsin to form the red photosensitive pigment. Under luminous excitation, *neo*-retinene is transformed into the yellow, all *trans* isomer and

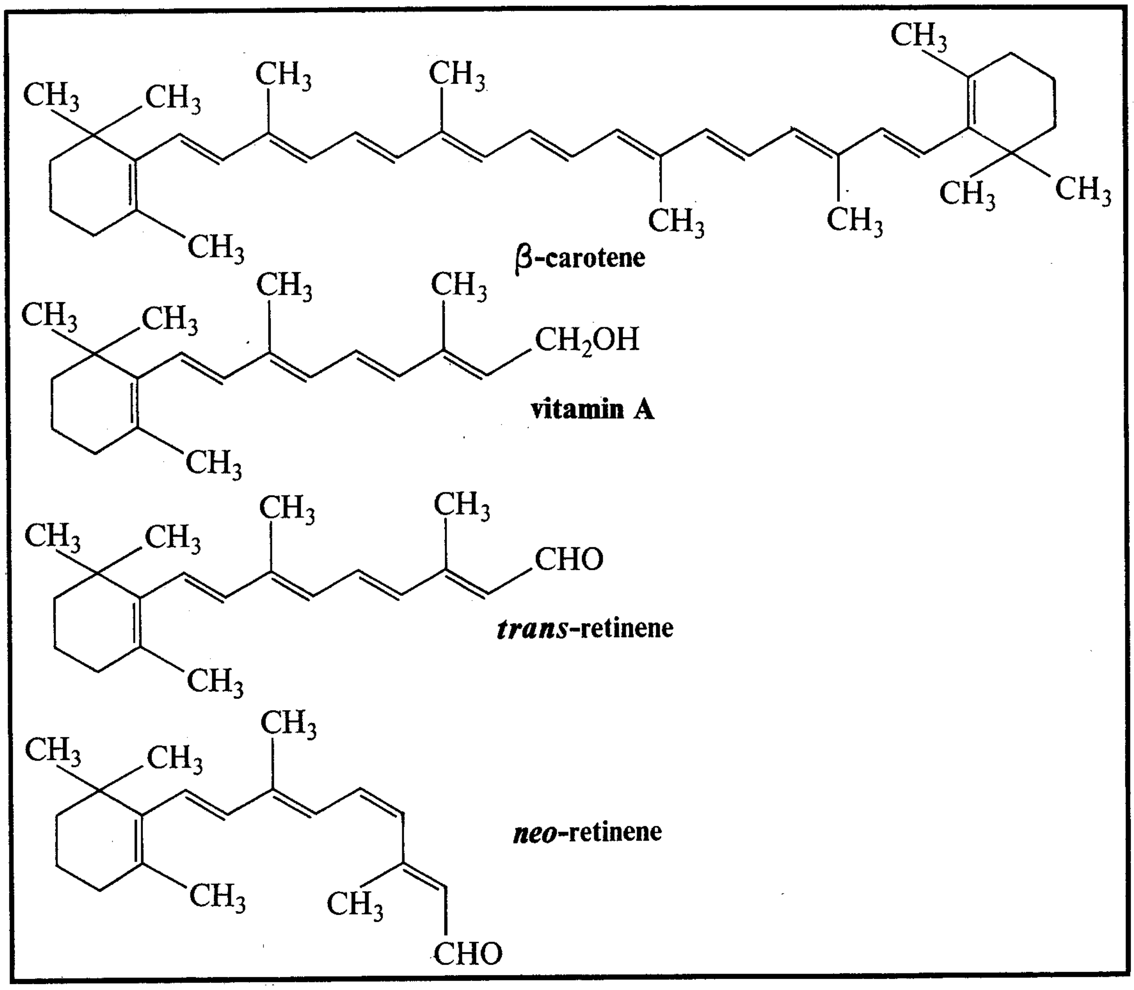


Fig. 119 **Formulae of compounds related to the chemistry of vision. From the top, β-carotene, vitamin A, *trans*-retinene and *neo*-retinene. The latter two compounds are stereoisomers of the *cis-trans* type. The high degree of unsaturation in these molecules makes them sensitive to electromagnetic radiation with a wave-length between 400 and 700 nm.**

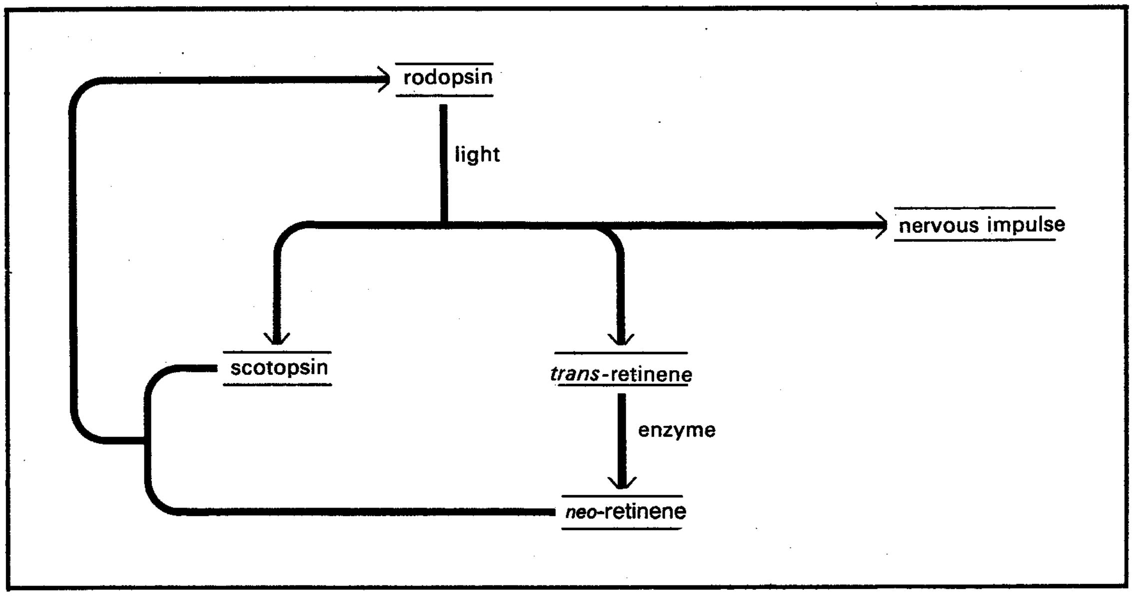


Fig. 120 Under the action of light rodopsin splits into a protein (scotopsin) and *trans*-retinene; at the same time, a nerve at the back of the eye is stimulated. *Trans*-retinene is then converted into *neo*-retinene which combines with the protein to form rodopsin. The regeneration of rodopsin occurs quite slowly; for this reason intensive lights at night produce dazzle.

simultaneously it separates from the protein. Most probably the nervous impulse which reaches the brain has its origin in this phase. Retinene is next transformed, under the action of an enzyme, into *neo*-retinene and this in its turn recombines with scotopsin to complete the cycle (Fig. 120). The explanation of the chemical process of vision is chiefly due to the American biologist George Wald who was awarded the Nobel prize for medicine in 1967.

An analogous mechanism has also been discovered for vision in full light. This takes place by means of the cones. The lower sensitivity is accompanied by a broader visible spectrum and gives a greater ability to discern shapes and colours. In addition to the different morphology of the sensory elements, these properties also depend on the different constitution of the protein conjugated to retinene

It is well known that vitamin A has a supporting effect on the therapy of illnesses of vision and is necessary for good night-vision. The chemical relationship between vitamin A and retinene is quite close. It is an oxidation-reduction alcohol-aldehyde like that described in the preceding paragraph and is regulated by the coenzyme NAD. It has been found that vitamin A is closely related to the carotenoids, yellow substances contained in numerous vegetables. In a certain sense it is possible to say that plants also possess an elementary form of vision, the so-called phototropism or the capacity to orientate themselves according to luminous stimuli. Certain flowers open with the dawn light and close again at sunset, and the golden head of the sunflower rotates to follow the movements of the sun. These movements can be attributed to the photosensitivity of carotene and to processes analogous to those occurring in retinene. The response of the sunflower is certainly much less precise and detailed than the response of, say, the eagle, but it has a similar chemical basis. The mechanisms function so well that it has resisted evolutionary processes, undergoing only some minor modifications at the molecular level.

IX

The origin of optical activity

'We will start from the assumption that *life cannot and never could exist without molecular dissymmetry* . . . . How could the molecular dissymmetry of the original protoplasm . . . . have arisen without the intervention of life?'*

'I shall try to develop the thesis that optical activity appeared as a consequence of intrinsic structural demands of key molecules of which organisms were eventually composed, through the selection of optical isomers from racemic mixtures.'†

'I am informed . . . . that there is still widely believed to be a problem of explaining the original 'asymmetric synthesis' giving rise to the general optical activity of the chemical substances of living matter. I have long supposed that this was no problem on the basis of a supposition that the initial production of life is a rare event.'‡

We have presented these very contrasting statements to illustrate how uncertain and contradictory are the views on the subject with which we shall now deal: the origin of optical activity on Earth. Optical activity is obviously very much related to the problem of the origin of life and in this matter many opinions are really based on hypotheses, made *a priori,* which often do not take into account all the experimental facts. The fundamental preoccupation seems to be to try to justify these hypotheses by adducing suitable evidence to fit them, rather than the other way about.

However, if the taboos and mythology which confuse these problems are eliminated, it becomes evident how much space there is for scientific enquiry, even if it is not always possible to apply the usual techniques of experimental research, and chemical research in particular. There is obviously a difficulty in obtaining adequate

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*A. P. Terent'ev and E. I. Klabunovskiĭ, in *The Origin of Life on the Earth,* papers of the congress held at Moscow in 1957, Pergamon Press, 1959, p. 95.

†G. Wald, *Annals of the New York Academy of Sciences,* **69** (1957), p. 358.

‡F. C. Frank, *Biochimica et Biophysica Acta,* **11** (1953), p. 459.

experimental verification. If the crust of the earth solidified about five thousand million years ago and if the first forms of life arose a little less than one thousand million years ago, the time available for certain processes to evolve in the desired sense (with the hypothesis that the origin of optical activity belongs to the pre-biological as well as to the biological epoch) is absolutely out of proportion with the normal duration of our experiments. In addition, if it is wished to carry out accurate experiments on the subject in the world of today, it is necessary to be able to eliminate any influence which may come from the numerous existing optically-active compounds (mould in water, atmospheric dust, the presence of the human worker himself). For these reasons the study must essentially be based on models. Hypotheses are thus indispensable but their limits must be very clear. It is necessary to know just how far the discussion still has significance and where it has become an academic exercise or a gratuitous speculation.

On these bases let us try to see what facts can be considered as certain, which hypotheses can reasonably be expressed and which experimental data are in favour of one hypothesis or the other.

The fact that living species are composed of optically active molecules depends on the complexity of such molecules and on an economic criterion which can be attributed to nature. The more the complexity of a molecular species increases the more likely it is to be dissymmetric, that is to say, not to possess those alternating axes of symmetry which are necessary conditions for optical inactivity. If, in particular, we consider the natural macromolecules, the phenomenon becomes still more obvious. In the macromolecular field the factors of diastereoisomerism and the existence of regular dissymmetric conformations (like helices) make steric selection absolutely necessary.

A cellulose made from D-β-glucose and L-β-glucose units randomly distributed would be formally analogous to an atactic polymer, radically different chemically, physically, biologically and mechanically from the corresponding isotactic polymer, and it would probably have none of the properties which make cellulose one of the fundamental constituents of vegetable tissue. Structural reasons thus require that living organisms must be formed from molecular species precisely defined on the stereochemical plane.

However, there is another aspect of the problem. Why are there not two celluloses, both sterically pure and formed respectively from D-β-glucose and L-β-glucose? Or why are there not two types of protein, one with L amino acids and the other with D amino acids? Such a situation would require a double mechanism of synthesis. There would have to be, for example, two types of DNA, one formed from *dextro-* and the other from *laevo*-deoxyribose, to synthesize the two enantiomorphous proteins. The metabolic processes would then be extremely complicated: what use could an organism of a certain sign (or that part of an organism which had a certain sign) make of substrates suitable for its enantiomorph? A doubling of functions and reactivities would be created at all levels, molecular, cellular and so on. It is known that this does not occur, at least in the higher organisms. Nature has simplified affairs in favour of greater efficiency. But how can all this have happened?

The abiological hypotheses

The hypotheses on the origin of optical activity are at different levels and it is difficult to give a simple and logical picture of them. We shall start from what is, in our opinion, the fundamental question: is there an intrinsic asymmetry in the universe and is it efficient at the molecular level?

A critical examination of the symmetry properties of physical phenomena was made by Pierre Curie in 1894. He showed, for example, that a gravitational field possesses reflective symmetry elements and, consequently, cannot produce dissymmetric effects. The same is true for a magnetic field.

A potential case of asymmetry is provided by circularly polarized light. At the beginning of this book we spoke of another type of polarized light, that in which the plane of vibration of the electromagnetic wave is fixed (linearly polarized light). With a contrivance often used in physics, an alternating linear movement can be converted into circular movements (a mechanical example being provided by the conversion of the alternating motion of a piston into the circular one of the automobile crank shaft). Linearly polarized light can be considered as the resultant of two light rays with equal phase and intensity in which the plane of polarization is not fixed but rotates continuously in opposite senses, left and right (Fig. 121).

In circularly polarized light, which can easily be obtained by using special sheets of mica, called quarter-wave sheets, the electric and magnetic vectors describe helices in space and the symmetry characteristics of such radiation can influence molecular phenomena. A photochemical reaction, that is to say one promoted by light, on a prochiral or racemic substance, in the presence of circularly polarized light of suitable wave-length, can induce a certain optical activity. This was observed for the first time by Werner Kuhn in 1930 and subsequently confirmed by several researchers using other examples. The process is often called absolute asymmetrical synthesis. The use of such a phrase indicates that no dissymmetric

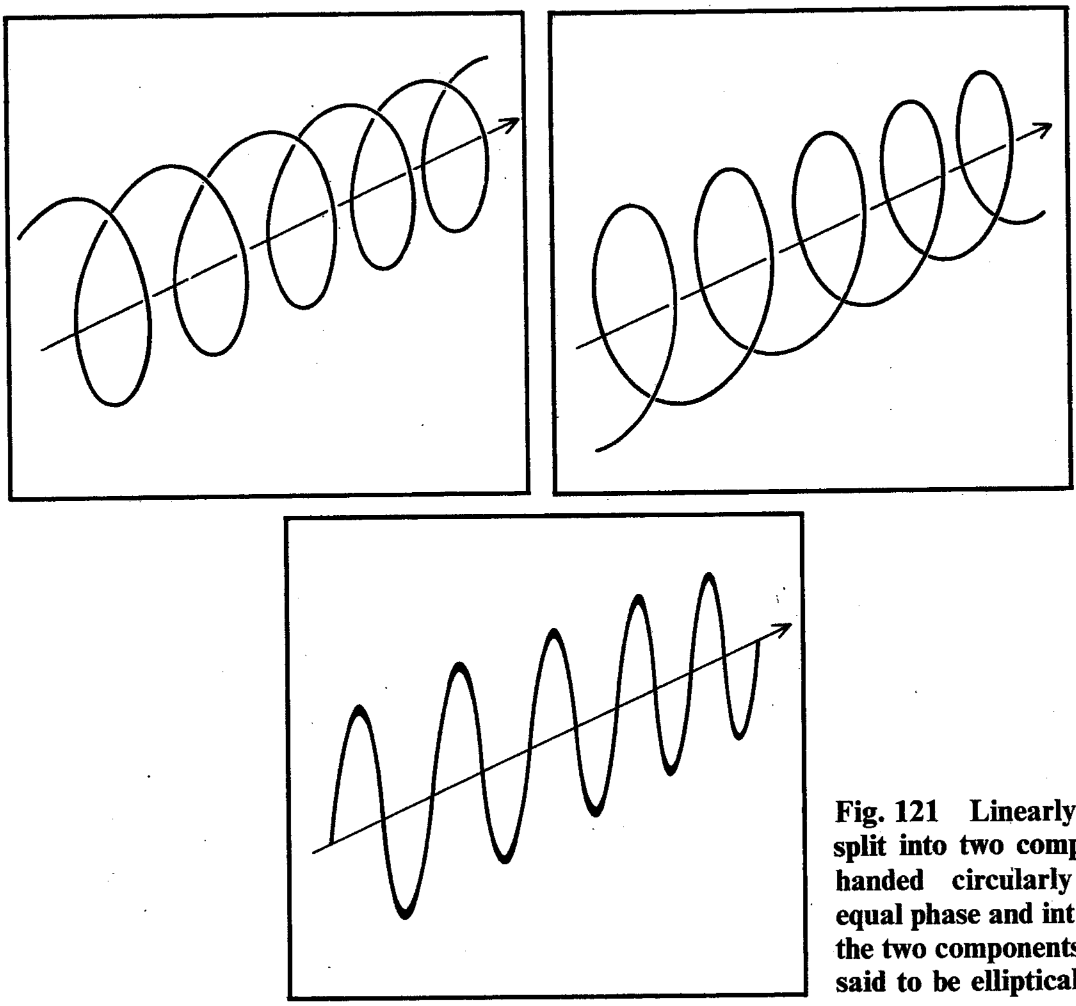


Fig. 121 **Linearly polarized light can be split into two components: left- and right-handed circularly polarized light with equal phase and intensity. If the intensity of the two components is not equal, the light is said to be elliptically polarized.**

chemical was used to induce the asymmetry in the product but only a physical agent (the polarized light).

The interest of these experiments is considerable, since scattered and reflected solar light are effectively polarized in certain conditions and, according to some rather old bibliographical references, there is a slight preference for the right-handed component over the left-handed (the light, therefore, being elliptically polarized). Verification of these results (it must be determined whether the ellipticity is derived from *originally* natural causes and not from the asymmetric nature of the reflection planes – life and thus optically active compounds are spread everywhere over the earth and in the sea) seems necessary before this hypothesis can usefully be taken into consideration.

Recently, another fundamental dissymmetry was discovered by Lee and Yang in the weak interactions between particles, where the principle of conversation of parity (one of the fundamental postulates of physics) was found to be no longer valid. As a consequence of this discovery, it was argued that certain β radiations (consisting of electrons), such as those from ^{32}P, are polarized and so also are the *Bremsstrahlungen* obtained from these through collision with other particles. (Bremsstrahlungen literally means braked radiations: they are electromagnetic radiations, generally of the γ type but which can have lower frequencies and therefore much lower energy.)

Yet the degree of circular polarization depends on the energy of the slowed radiation and it can be shown that in the area of energies useful for promoting chemical processes the ellipticity is extremely low and practically negligible. The experiments which have been carried out on this matter have not yet given any clearly affirmative result.

Before concluding this exposition, it is necessary to ask whether or not there are some chemical indications of the presence of a fundamental asymmetry outside the biological world. The literature on the topic is controversial. It has been reported, for example, that dextrorotatory quartz is more abundant in nature than the laevorotatory form but the degree of this over-abundance is highly dubious. A very surprising result was reported concerning certain complex salts such as the silicododecatungstate of potassium $K_4[SiW_{12}O_{40}]\cdot 18H_2O$ and its isomorphs. These crystallize from water in a hemihedric (dissymmetric) way. Of the two possible forms, always and only the dextro is obtained through spontaneous crystallization, that is to say, without adding pre-formed crystals. Is this an amazing demonstration of natural asymmetry or does it arise from insufficient experimental care with regard to possible impurities? The problem is open and needs reinvestigation.

An analogous phenomenon was studied by the Dutchman Havinga in a much more rigorous manner. Among the salts of tetrasubstituted ammonia which exist in enantiomorphic forms (tetravalent nitrogen has the same stereochemical properties as carbon), methylethylallylphenylammonium iodide, although optically inactive in solution, crystallizes quite easily into dextro or laevo enantiomorphic crystals (Fig. 122). The two optical antipodes are stable in the solid state but not in solution, where a rapid inversion of configuration is observed. A series of samples of this salt left to crystallize for a long time in sealed tubes produced in the great majority of cases the positive optical antipode, at other times the racemic product but never the negative optical antipode. The experiments might have seemed sufficient and the conclusions quite obvious to a less attentive researcher; but when the experiments were repeated in a more careful way, trying to avoid possible causes of impurity, the results were totally different. The trials resulting in a negative sign equalled those giving a positive sign. Even though the statistical sample was not large (only seven trials) the conclusion drawn by Havinga seems to us fully justified. This is really a spontaneous asymmetric crystallization and demonstrates the possibilty of obtaining optically active substances without

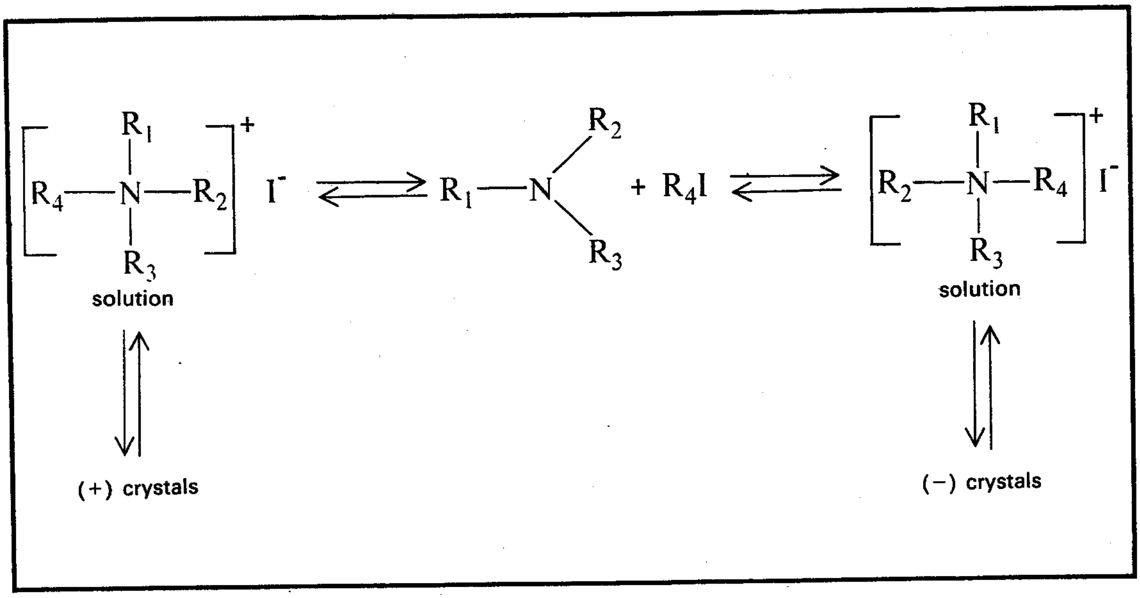


Fig. 122 Tertiary amines react with alkyl iodides to give quaternary ammonium salts. If the four alkyl groups bonded to the nitrogen are different to each other, there is a phenomenon of enantiomorphism analogous to that existing in carbon compounds. In the case examined by Havinga, the two optical antipodes easily interconvert in solution but crystallize in optically pure forms. The racemic solution can be converted into one or the other of the optical antipodes in a purely random fashion.

external intervention by starting from inactive material in a closed system.

The experiments just described introduce us to an alternative hypothesis for the origin of optical activity: that of the random event, unique or at least rare. Statistical laws are normally valid only for large amounts of data and the average properties of a restricted sample can be very far from the average properties of the whole population from which it is taken. In samples normally used in chemical research (a few milligrams of a substance contain more than 10^{20} molecules) phenomena are statistically compensated and the excess of some, or even some thousands, of molecules with one sign does not cause, under normal conditions, any observable lack of compensation. But if the system is drastically reduced in dimensions and the reaction occurs, in the limit, to only one molecule, the result can only be dextro or laevo. On the hypothesis that a similar reaction is quite rare and that the product rapidly produces a series of asymmetric reactions on other molecules, or even that it is an autocatalyst (a catalyst for the formation of molecules similar to itself), it is possible to visualize a spontaneous asymmetric production of certain molecular species. A case of this type could be represented by asymmetric crystallization as described by Havinga, by means of successive asymmetric reactions which occur on the surface of a crystal.

Asymmetric syntheses or decompositions on crystals of quartz have already been described by numerous authors, but with low optical yields. We know that quartz exists in nature in two optically active forms. If it happens that a dextro crystal finds itself by chance in a particularly reactive surrounding, a chain of asymmetric reactions might be intitiated without the formation of the corresponding optical antipode.

Fundamental asymmetry or chance event: how to decide on one or the other hypothesis? In order to reply it is necessary either to enquire in depth into the real incidence of the presumed causes for the origin of asymmetry, or to be able to examine a vast sample of optically active compounds from other planets, assuming that forms of life analogous to those on Earth, at least at the molecular level, occur widely in various galaxies.

The biological hypotheses

George Wald and many others deny that there is any validity in the preceding theories. The inorganic or, better, non-biological sources of optical activity – he says – all have the same faults: very restricted reaction conditions, limited field of operation, low yields and the almost total tendency to give only local and temporary asymmetries. The alternative thus lies between two hypotheses: is optical activity a necessary factor for life or is it a consequence of it? Does its origin belong to the pre-biological epoch or rather to the biological?

The evidence that is given in favour of the biological hypothesis was largely suggested at the beginning of this chapter and lies in the complexity and structural regularity existing in biological molecules. This regularity is, however, essentially based on the phenomenon of diastereoisomerism and not on asymmetry in the strict sense; the dextro or laevo problem still remains unsolved at this point. The door is open to several possibilities: the choice between (+) and (–) is due to a unique and chance event (the last hypothesis of the preceding paragraph carried over to the level of elementary organisms) or it arose from a struggle in evolutionary terms between two opponents. The species which succeeded and survived, by chance or by virtue of some external help (polarized light?) then spread over the whole earth; in which case the possibility that the enantiomorphic species could originate again and develop became absolutely negligible. The molecules of which an organism is composed are connected to each other by a complex series of relationships; the fact that the nucleic acids were of the D series requires the synthesis of L proteins. These are hydrolysed by enzymes containing amino acids of the L series. In its turn, the co-enzyme ATP, the carrier of energy in the majority of biological reactions, contains a D sugar, like the DNA at the beginning. Thus one can explain the formation of a completely self-consistent system such as that which today exists in the higher organisms. The problems of nutrition and assimilation, moreover, require that this coherence should also exist between different organisms.

As experimental support for this idea, the fact can be mentioned that some micro-organisms quite low in the phylogenetic scale still contain amino acids of the D series. In addition, in the higher organisms some phenomena (for example, the presence of a specific enzyme for the wrong series) are found which are interpreted as vestiges of that primitive struggle.

A third type of question may be asked, a question which crops up in different ways depending upon the reply given to the preceding questions. Did optical activity arise suddenly, having its maximum value right from the beginning (on a statistically significant sample) or did it evolve progressively, only reaching purity after many processes?

If one accepts the hypothesis of a unique or very rare event at the molecular or biological level (for example, a very high yielding asymmetric synthesis or the union of a homogeneous group of molecules endowed with the property of reproducing themselves, even if in a very primitive way) and if all the forms of life originate in some way from that event, the first solution is possible even it it is unnecessary.

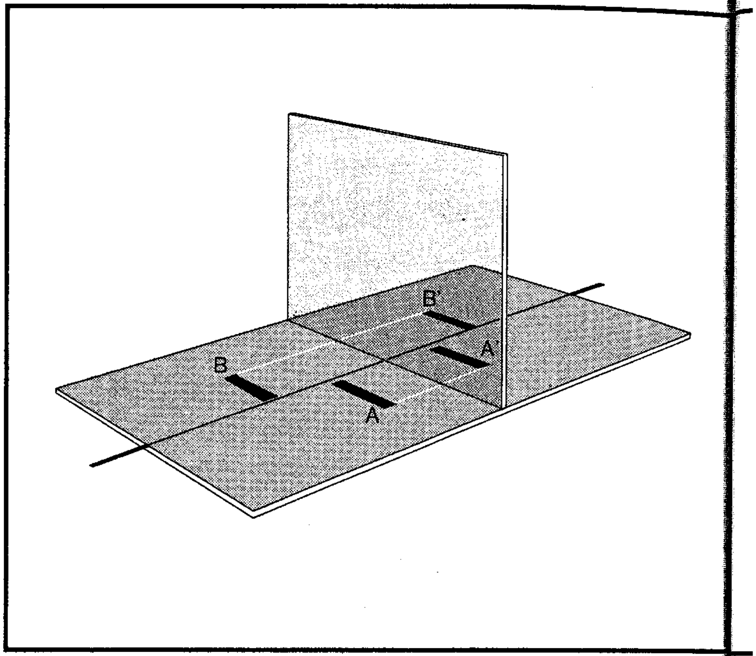


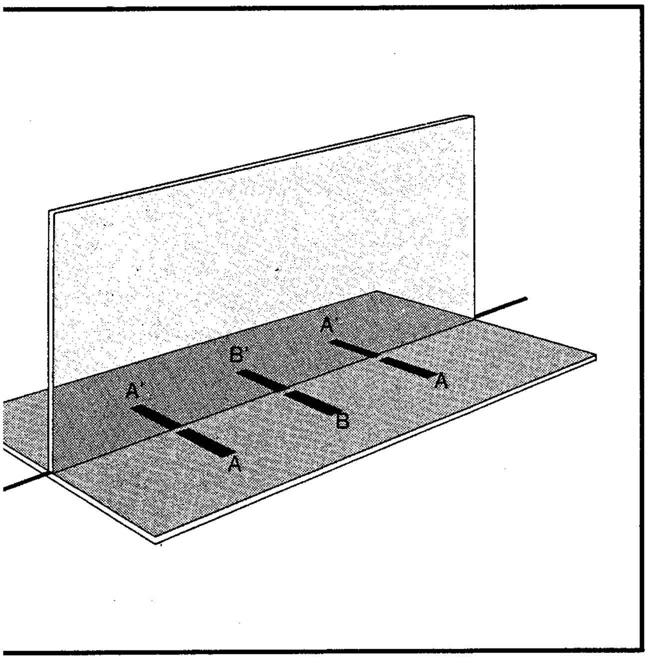
Fig. 123 In addition to the symmetry elements described in chapter IV, it is also necessary to consider for macromolecules planes of symmetry combined with translation. These planes are characterized by an operation of reflection and a translation along an axis lying in the plane. From the left, diagrams of a symmetry plane perpendicular to the axis of the polymeric chain, of a symmetry plane containing the axis of the chain and of a glide plane containing the axis of the chain.

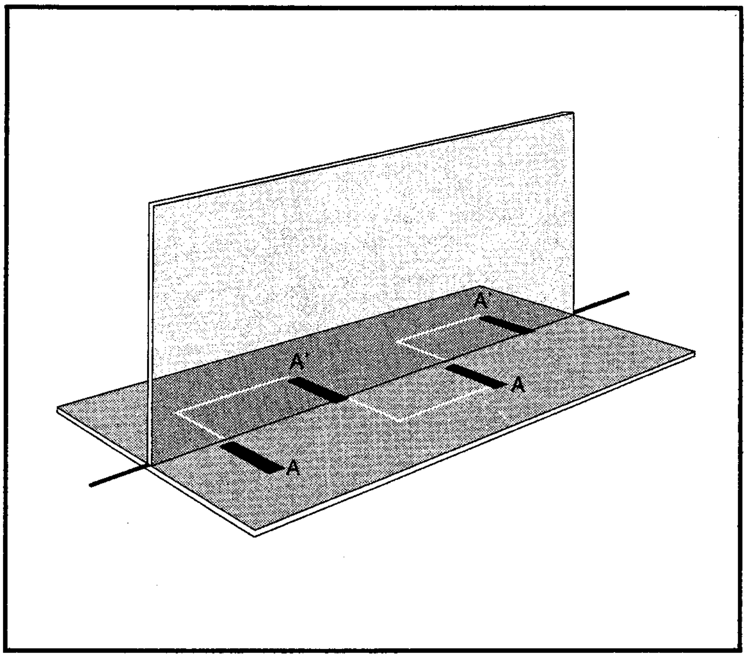
In the alternative case, it is necessary to hypothesize evolutionary processes of a chemical and biochemical type. The problem of autocatalytic syntheses arises here. In such syntheses the product of a reaction or one of the intermediates is a positive catalyst for the same reaction. With some simple probability calculations it is possible to show that with processes of this type, after a sufficient number of cycles, it is possible to reach practically complete stereochemical purity.

Some experimental verifications

The reader will have become aware that nothing very conclusive can be said at this point. Experiments are very often of doubtful value and are never definitive. There does not exist, in fact, an *experimentum crucis* capable of destroying one or another hypothesis. Before new conclusions can be reached it is necessary to conduct experiments which may last many years.

We would like to make a contribution, albeit limited, by mentioning a few results obtained in recent years in our laboratory. We should state immediately that the origin of optical activity is not a primary object of our research, which is more concerned with the phenomenon of asymmetric induction in macromolecules. However, some data found by us may help to clarify part of the wider problem.





It will be convenient to refer to some ideas already indicated in the previous pages. The processes of stereospecific polymerization have shown how important the phenomena of stereoisomerism are in the macromolecular field. Starting from propylene, it is possible to obtain two stereoregular but completely different polymers (isotactic

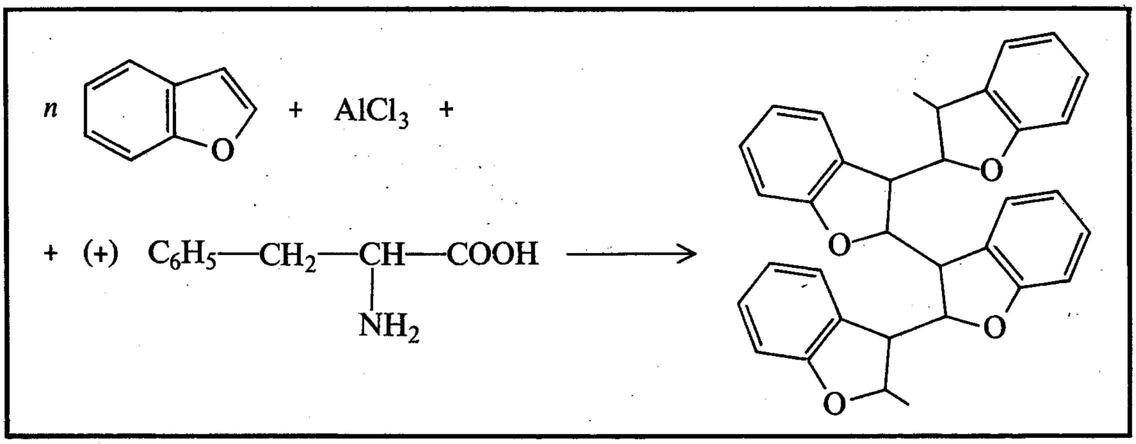


Fig. 124 Asymmetric polymerization of benzofuran. By the action of the asymmetric catalyst formed from aluminium trichloride and an optically active amino acid, phenylalanine, benzofuran is converted into a polymer endowed with a high rotatory power.

and syndiotactic polypropylene) and a whole range of polymers with intermediate, atactic, structures whose properties are much less interesting. The properties of the polymer depend very much on its steric purity which in the best samples is over 99 per cent.

In spite of its very high steric purity, polypropylene cannot exist in enantiomorphous forms and thus cannot be optically active. In the case of polymers the rules of optical activity are slightly different from the usual ones described in chapter IV because of the enormous length of the chain. A polymeric chain of infinite length can exist in enantiomorphous forms only when, in a Fischer projection, there are

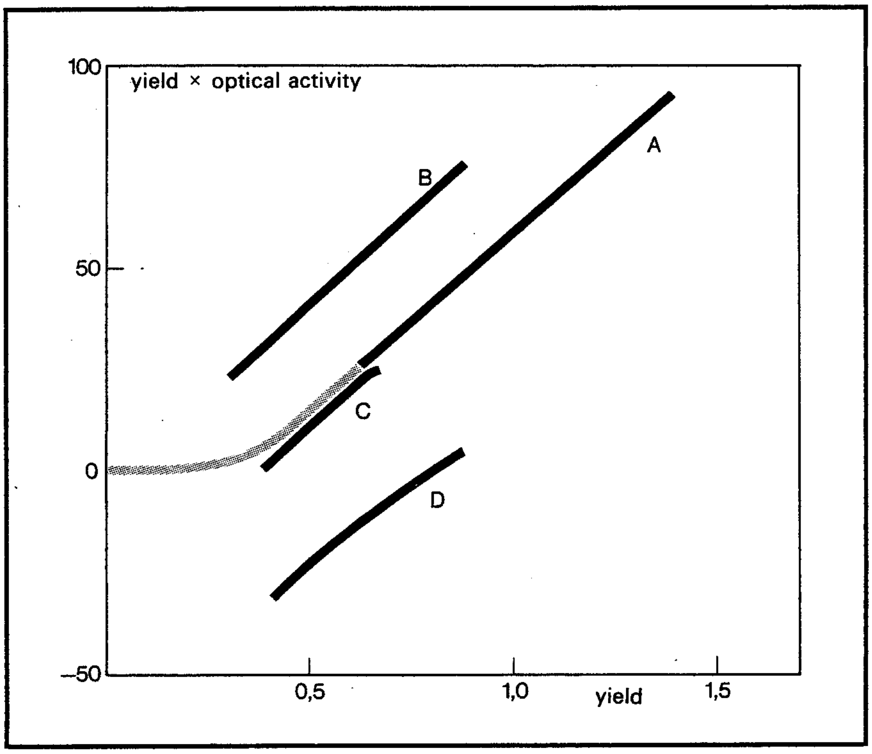


Fig. 125 Autocatalysis in the polymerization of benzofuran. At the beginning of the polymerization the optical activity of the polymer is very low and reaches appreciable values only after a certain quantity of the polymer has been formed. Experiments carried out in the presence of pre-formed polymer confirm the hypothesis of a modification of the polymerization process by the action of the polymer itself. In the diagram the abscissa shows the polymer yield and the ordinate shows (polymer yield × rotatory power). The value of the optical activity of the polymer is proportional to the slope of the curve. The fact that the lines are parallel indicates that the polymer which is formed has the same rotatory power in all cases, independently of the optical sign of the polymer introduced at the start.

no planes of symmetry perpendicular to the chain nor planes of symmetry with translation which contain the chain (glide planes) (Fig. 123).

Polymeric structures which satisfy such conditions and which at the same time can be obtained by starting from non-dissymmetric monomers are very few; but two of these were synthesized by us in 1960–1961. The processes, although chemically quite different in the two cases, were based on the same principle, the use of an optically active catalyst. One of the two directions of growth of the chain is favoured over the other and the resulting polymer is optically active. We have been able to show in the case of the polymerization of benzofuran that the asymmetric catalyst (consisting of a complex between aluminium trichloride and an optically active amino acid, phenylalanine) reacts in each stage of the polymerization like a template which ensures that the incorporation of the new monomer always occurs in the same configuration (Fig. 124).

Thus far everything is in agreement with well-known principles, even if to have carried out a multiple asymmetric synthesis (for hundreds and hundreds of times) on the same molecule represents a new and certainly not negligible advance. But in some experiments, carried out under special conditions, a totally unexpected phenomenon appeared. The optical activity of the polymer which was slowly forming, increased from an almost zero value to about 80° and then progressively diminished. The interesting part of the observation

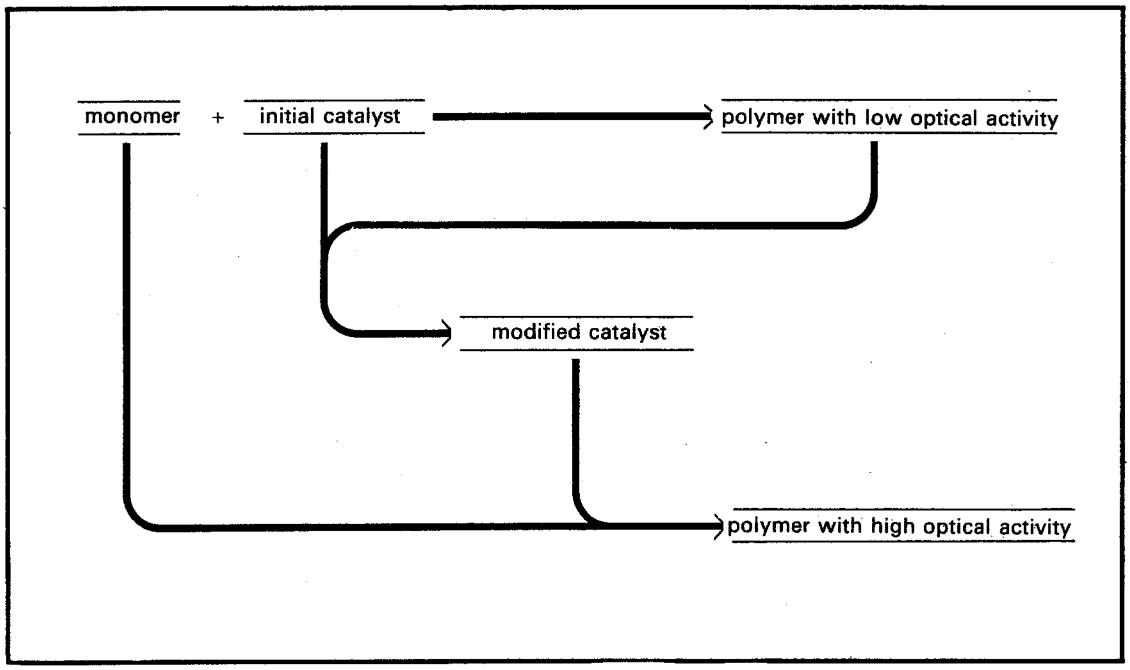
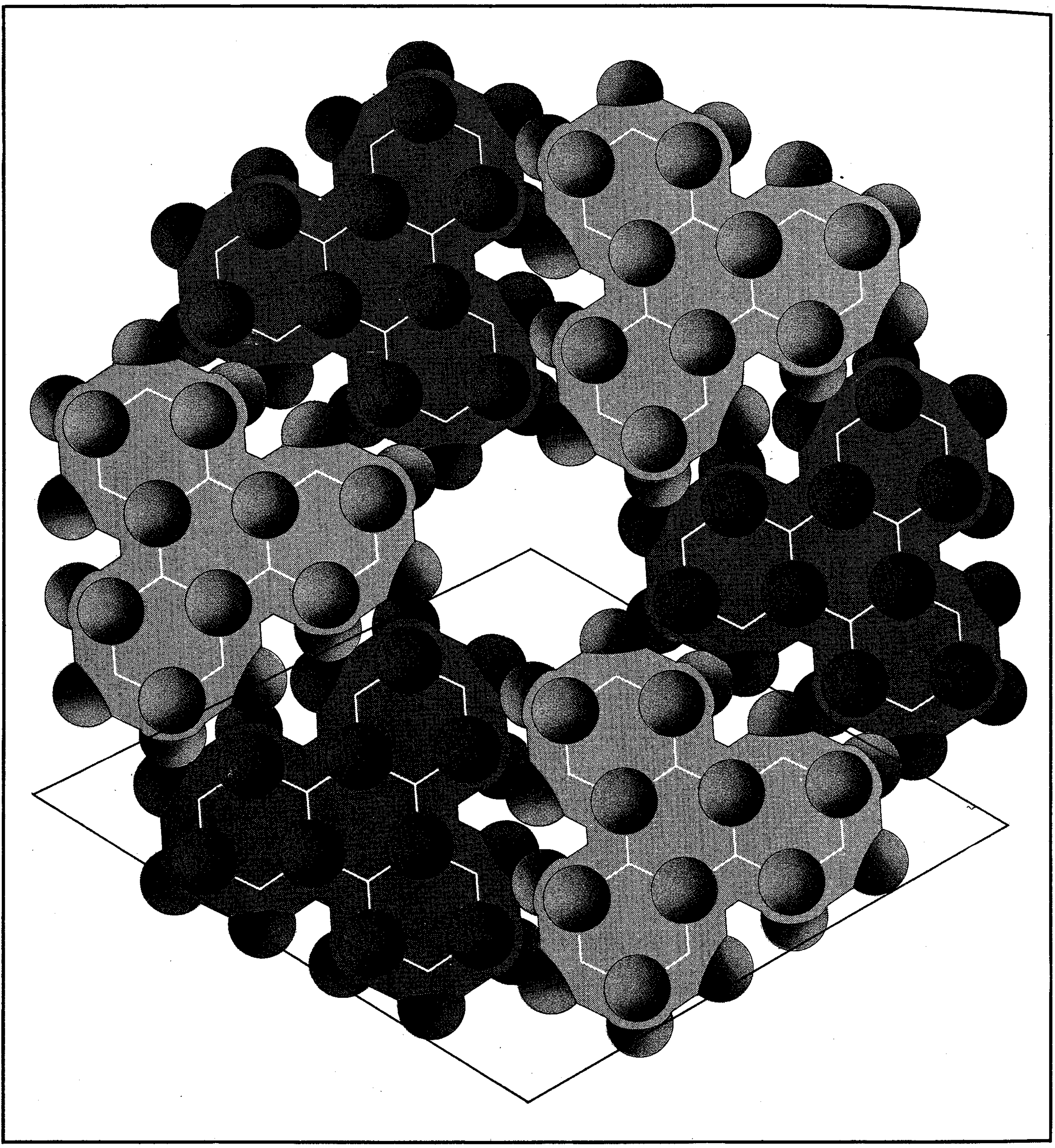


Fig. 126 **A scheme of the probable action of the polymer on the asymmetric polymerization process. While the initial catalyst has a mediocre power of induction, the modified catalyst from the polymer already formed is capable of inducing considerable asymmetry.**

is the initial increase in activity. How may it be explained? Among the plausible hypotheses, that of an asymmetric autocatalytic process was suggested. The polymer with low activity could have an effect on the asymmetry of the reaction, progressively raising the selectivity until maximum activity was reached. Faced with a possible explanation of this type it was necessary to proceed with the maximum of caution. The three types of polymer (dextro, laevo and



racemic), the symmetrical catalyst, and the catalyst required to produce the dextro polymer were then prepared and verification of the hypothesis begun by carrying out the polymerization in the presence of the catalyst and a quantity of the pre-formed polymer. With the optically inactive catalyst the result was as predicted: the product was racemic and the pre-formed polymer had not produced any apparent effect. But using the asymmetric catalyst, a new factor

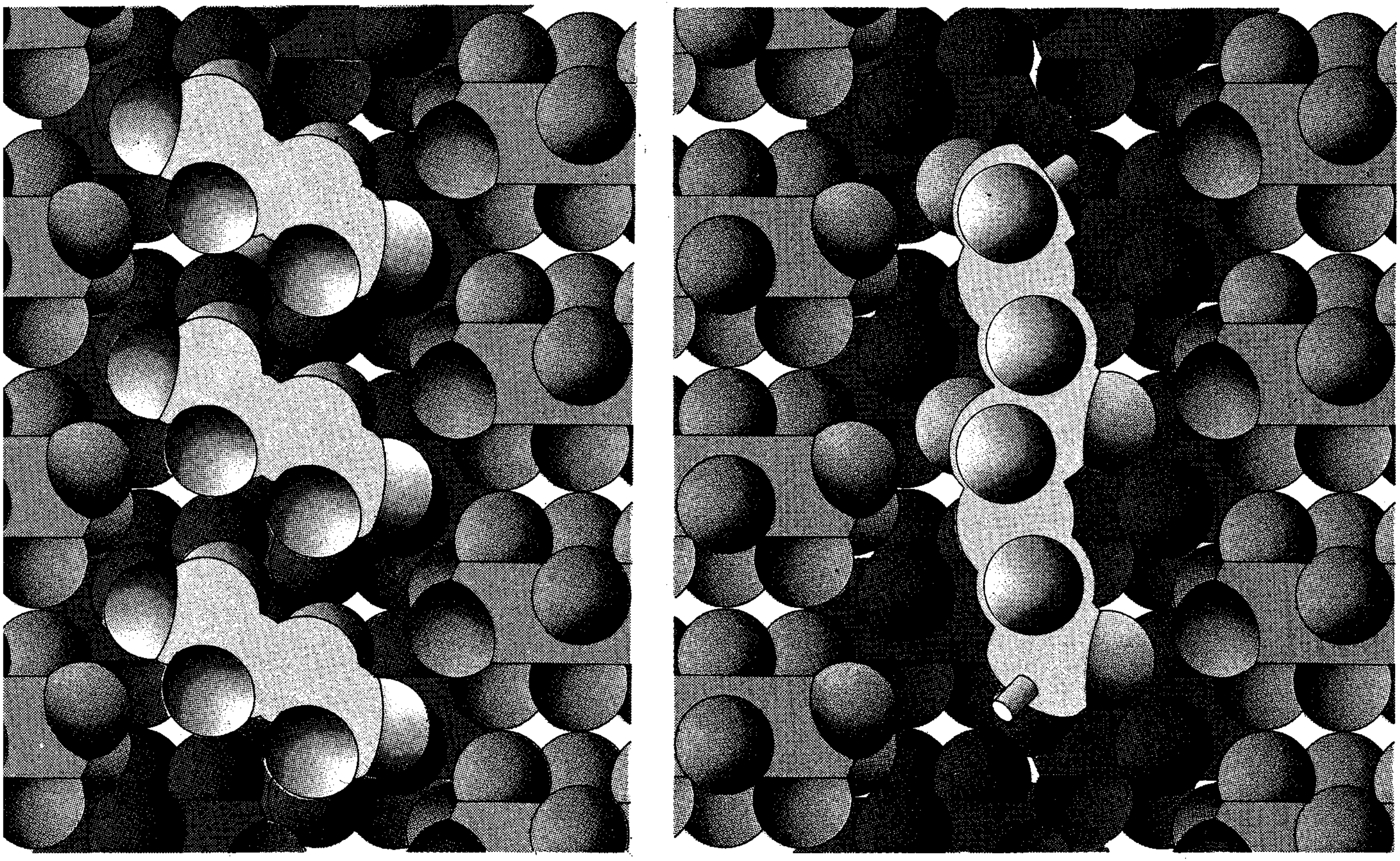
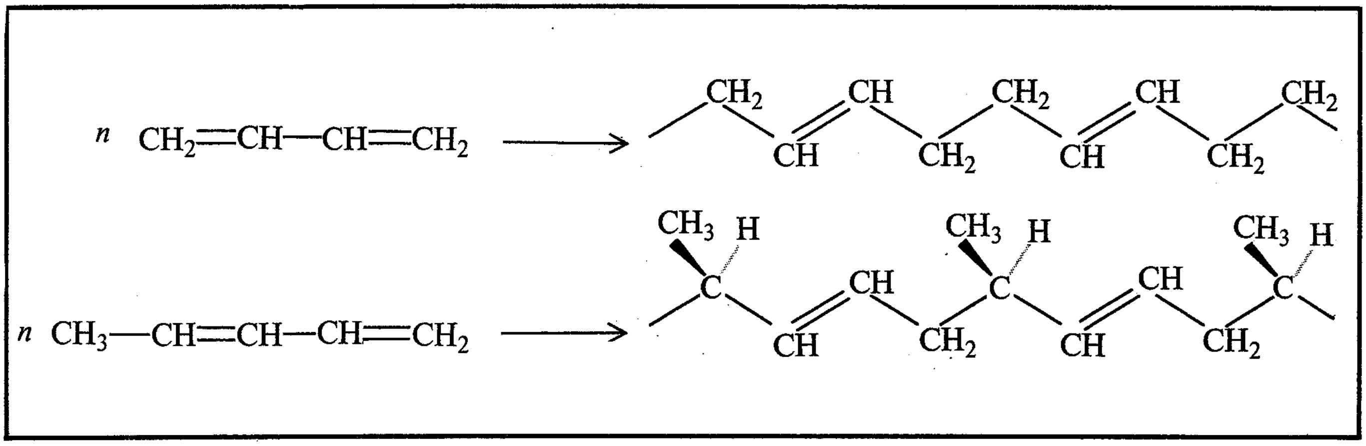


Fig. 127 On the left, the crystalline cell of perhydrotriphenylene. The external dimensions of the molecules are obtained by using spherical molecular models. At the edge of the crystalline cell a hole is observed where guest molecules can be held. Above, structures of the inclusion compounds, perhydrotriphenylene-butadiene (left) and perhydrotriphenylene-polybutadiene. Below, a scheme for the polymerization. The structure of the polymer is 1,4-*trans*. The asymmetric synthesis described in the text was carried out on pentadiene, the lower of the two formulae below. The corresponding polymer, of the 1,4-*trans* isotactic type, contains an asymmetric carbon atom in each monomeric unit.



came to light. In all three cases (with the pre-formed dextro, laevo and racemic polymer) the dextro polymer was immediately obtained with maximum steric purity. Its sign was uniquely determined by the asymmetric catalyst but the value of the rotatory power was determined by the presence of the pre-formed polymer, independently of of its optical sign (Fig. 125). In control trials carried out under the same conditions but without the preformed polymer, the optical activity reached maximum values only after a quantity of the polymer approximately equal to that present from the start in the other trial had been produced by the reaction.

The experiments just described seem to support in a significant way the idea of an autocatalytic action exercised by the polymer on the mechanism of the reaction itself (for example, by partially modifying the structure of the catalyst). Such an autocatalytic action is still not an asymmetric one in the real sense because it does not depend on the sign of the pre-formed polymer, but is such only in an indirect way because it raises the power of asymmetric induction of the catalyst (Fig. 126).

Another different but equally notable result was recently obtained. It concerns an asymmetric polymerization induced by the action of γ-rays on a monomer contained in a dissymmetric crystal.

We have already mentioned, in discussing starch, the ability of certain substances to form inclusion compounds or to act as hosts for other molecules in their own crystalline structures. One of these host substances was discovered and studied in depth in our institute. It is perhydrotriphenylene, a polycyclic hydrocarbon which crystallizes in a hexagonal form. In the crystals its molecules are arranged so as to form channels which can be filled by other molecules of a suitable shape; these should be relatively narrow and long, and linear macromolecules (like polyethylene) are particularly suitable.

When an inclusion compound between perhydrotriphenylene and a suitable monomer is subjected to γ-radiation, from a cobalt bomb, the included component polymerizes in a stereospecific manner (Fig. 127). Perhydrotriphenylene has a dissymmetric structure and can exist in optically antipodal forms (see Fig. 48, p. 101); its resolution, difficult and expensive, was recently carried out in our laboratory. With the optically active product it was desired to test whether an asymmetrical synthesis was possible. The result was that for which we had hoped: the polymer obtained was optically active.

Very probably it is the particular shape of the channel that determines the transition state of the asymmetric polymerization process. This method of obtaining optically active compounds seems to us particularly significant because of the drastic and apparently low selective conditions under which it is carried out.

How can these experiments be reconciled with the previously discussed hypotheses, in the light of the apparent contradiction? Asymmetric polymerization in the included state indicates (but does not confirm) the possibility of analogous syntheses in clay and other silicates capable of including reactive molecules (providing that there is in the system at least a chance of asymmetry). The autocatalytic process of benzofuran approaches closer to the biological processes and seems, in a certain sense, to resemble life itself (the growth followed by decrease in the optical activity). But our models consist only of hydrocarbons and other very simple compounds. We have neither examined proteins nor nucleic acids and our experiments are thus very far from reality; they are almost models of models.

Our research indicates that for an understanding of the origin of optical activity it may be better to concentrate attention on the macromolecular field. According to a theory we have recently proposed, asymmetrical macromolecular syntheses occur more easily than monomolecular ones, because of the co-operative effect due to the presence of the polymeric chain.

As we said in a previous chapter, living matter is formed largely from molecules having a high molecular weight. On the other hand, certain properties of synthetic polymers, such as the co-operative and autocatalytic phenomena, and the rigidity of macromolecular structures as conditions for the formation of more complex aggregates, seem to approach the complexity of the life process. Here one can perhaps find the point of contact between purely chemical behaviour and the biological. Certainly, a chemist will always tend to report phenomena at the molecular level while a biologist will see them in their more organized aspect. But is the contrast really irreconcilable? Was the primitive living organism nothing more than a particularly favoured macromolecule?

We shall not embark on this discussion but we shall leave it to be continued by those more competent to do so.

Appendix I

Emanuele Paternò and the theory of the tetrahedral carbon atom

The first document concerning the tetrahedral carbon atom appeared in 1869 in the *Giornale di Scienze Naturali ed Economiche* ('Journal of Natural and Economic Sciences') (Vol. V pp. 115–22) published in Palermo under the auspices of the Council for Improvement attached to the Regional Technical Institute (Consiglio di Perfeionamento annesso al Regio Istituto Tecnico). It was in the paper by Emanuele Paternò entitled 'On the Action of Phosphorus Perchloride on Chloral' and in an accompanying note written by Stanislav Cannizzaro.

Under the guidance of Cannizzaro, Paternò was investigating whether or not the four valencies of carbon were identical, a very exciting problem at that time because its solution would confirm or invalidate a great part of structural theory.

The two extracts we wish to present have been translated from the notes cited above. The only modifications concern the typographical expression of the chemical formulae. The actual name of dimethyl is ethane. First the statement by Cannizzaro:

'In dimethyl, CH_3-CH_3, two atoms of carbon are joined together, each of which carries three hydrogen atoms. I do not believe that there is any chemist (with the exception of Kolbe) who doubts that the two CH_3 residues bonded together are perfectly similar.

'There arises the doubt, however, whether the three hydrogen atoms connected to each carbon atom are similar to each other and of equal value. If they are of equal value, substituting a single atom of hydrogen of the dimethyl by chlorine can only lead to one body. Similarly there can only be one substance if five chlorine atoms are substituted and only a single hydrogen atom is left, i.e., only one C_2H_5Cl and one C_2HCl_5 can exist. If, instead, there should exist a difference between each of the three hydrogen atoms connected to each carbon atom, then there should be three isomers with the composition C_2H_5Cl and three with the composition C_2HCl_5. I say three isomers assuming, as there is no doubt, that the two CH_3

residues are perfectly similar to each other.

Notwithstanding that chemists may tend to assume the similarity of the different hydrogen atoms connected to the same carbon atom, some experiments have led to the belief in the existence of more isomer bodies with the composition C_2HCl_5. In one of these works presented by myself, Sig. Paternò demonstrates the identity of these bodies prepared by different routes and thus confirms the idea of the similarity of the three hydrogen atoms connected to the same carbon atom.'

Ethyl chloride C_2H_5Cl and pentachloroethane C_2H_5Cl were two fundamental points of this demonstration; but other facts were also advanced against the hypothesis of the equivalence of the hydrogen atoms. One of these was provided by dibromoethane $C_2H_4Br_2$, which was said to exist in three different isomers. This statement is mistaken: there are only two isomers of dibromoethane, the 1,1-dibromoethane CH_3-$CHBr_2$ and the 1,2-dibromoethane CH_2Br-CH_2Br. Since the existence of three isomers had been suggested, it was necessary to assign an adequate formula to them. Retaining the principle of the equality of the four carbon valencies, Paternò interpreted the structure of the three isomers (if these really existed, something which he himself doubted) with a tetrahedral arrangement of the bonds. As seen from the original drawing, shown by us on page 21, the two isomers of 1,2-dibromoethane are none other than the two conformers or conformational isomers obtained by rotation of one tetrahedron around the other (see chap. III).

Paternò's style of writing is rather direct and critical:

'. . . one of the fundamental principles of the theory of the constitution of organic compounds, based on the atomicity of the elements and particularly on the notion of the tetra-atomicity of carbon, is that of the identical chemical function of the four valencies of the carbon atom, which is not possible unless there exists only one methyl chloride, one methyl alcohol, etc. Now the existence of isomers for compounds of the formula C_2HCl_5 cannot be explained without renouncing the idea of the equivalence of the four affinities on the carbon atom. And this is the only example known until now that is opposed to such a generally adopted idea. As for the three $C_2H_4Br_2$ isomers, given that they really exist, they are easily explained without having to assume a difference between the four affinities of the carbon atom, as Butlerow believes, when the four valences of the atom of this element are assumed to be arranged in the sense of the four angles of a regular tetrahedron. Then the first modification would have the two bromine atoms (or any other monovalent group) connected to the same carbon atom; while in the other modifications each of the two bromine atoms would be bonded to a different carbon atom, with only the difference that in one of the two cases the two bromine atoms would be arranged symmetrically but not in the other. This is made clearer with the following drawings* in which the bromine atoms are represented by a and b.'

One might ask why, starting from these premises, Perternò did not reach the concept of the asymmetric atom before van't Hoff. We do not have any documents concerning this and can only try a conjectural reconstruction.

For Paternò the tetrahedral atom was only a chance hypothesis which permitted the principle of equivalence to be saved, even if there were three dibromoethane isomers and not two as there actually are. What escaped him was the relationship between that hypothesis and the phenomena studied by Pasteur concerning the optical activity of tartaric acid.

In his note of presentation Cannizzaro seems to call attention to the importance of this hypothesis and the possibility of that which we today call conformational analysis. Indeed he announced a programme of research in this direction. Unfortunately, the techniques of investigation then existing did not allow any positive results to be obtained. The ease of rotation around the bonds ensured that only in a few cases (and not in the simple compounds derived from ethane) were the conformational isomers stable and capable of being isolated.

The discussion started at Palermo in 1869 had no sequel. Rapidly overtaken by van't Hoff's theory of the tetrahedral atom, it was too tenuous and too far ahead of its time to be acceptable. And when conformational isomerism was discovered and experimentally verified, it was on completely different grounds.

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* The drawings are shown on page 21.

Appendix II

The nomenclature of optical stereoisomers

For each optically active compound it is possible to ascertain the absolute configuration, that is to say, the spatial arrangement of the substituents around the asymmetric centre (quite often an asymmetric carbon atom). This result is obtained by chemical methods, such as the transformation of one compound into another, whose configuration is already known, using reactions with an unequivocal and known route, or by physical methods such as circular dichroism. The possibility of obtaining the absolute configuration rests on the correctness of the spatial formula of (+)-glyceraldehyde proposed by Fischer, as proved by Bijvoet's experiment.

For each stereoisomer it is therefore possible to define the sign of the optical rotation (+) or (−) (observed under given experimental conditions) and the type of configuration, represented in a conventional manner. In the text we have generally used the D and L nomenclature, according to which all compounds whose formulae can be connected to that of positive glyceraldehyde belong to the D series and their optical antipodes to the L series.

This convention is very useful both because it is simply related to experimental facts (in many cases the individual enantiomorphs can be converted into D- or L-glyceraldehyde) and because it has allowed the recognition of some well defined series in the natural compounds (e.g., the D series of the sugars and the L series of the amino acids). However, in some cases such a convention leads to ambiguous results because of the equivocal relationship between the substituents of the asymmetric carbon in glyceraldehyde and in the compound under examination. An example of the inadequacy of this nomenclature is provided by tartaric acid whose positive optical antipode can be correlated both with the L and the D series (Fig. 128). It is as well to observe that this does not arise from an ambiguity in the knowledge of the absolute spatial structure of this compound but only from a different application of the conventional rules of nomenclature.

To overcome these difficulties a new system of defining stereoisomers was recently proposed which is independent of any relationship with other compounds.

In the *RS* nomenclature of Cahn, Ingold and Prelog, the arrangement of the substituents around the asymmetric atom is examined independently of the relationship of the compound with glyceraldehyde or any other standard. Such substituents are first arranged in a large-medium-small-smallest sequence (L-M-S-H, the smallest substituent very often being a hydrogen atom) according to the atomic number of the element bonded to the asymmetric atom. When two or more substituents are bonded to the asymmetric atom through identical atoms, the atomic number of the successive atoms is considered until each substituent is differentiated. For example, in the CH_3-group the carbon atom has atomic number (Z) equal to 6 and is bonded to three hydrogen atoms ($Z=1$). In the CH_3-CH_2-group on the other hand the first carbon atom ($Z=6$) is bonded to two hydrogens ($Z=1$) and to one carbon ($Z=6$) and, consequently, precedes the CH_3- group; the *iso*propyl group, $(CH_3)_2CH$-, similarly precedes the ethyl group, CH_3-CH_2-.

More detailed rules govern the order of precedence of isotopes (e.g., deuterium precedes hydrogen), of double bonds (*cis* precedes *trans*), stereoisomeric substituents (*R* precedes *S*) and other particular cases.

The order in the sequence of numerous common substituents is given in Fig. 129.

Having determined the sequence of substituents, it is possible to proceed to an assignment of the configuration by observing the

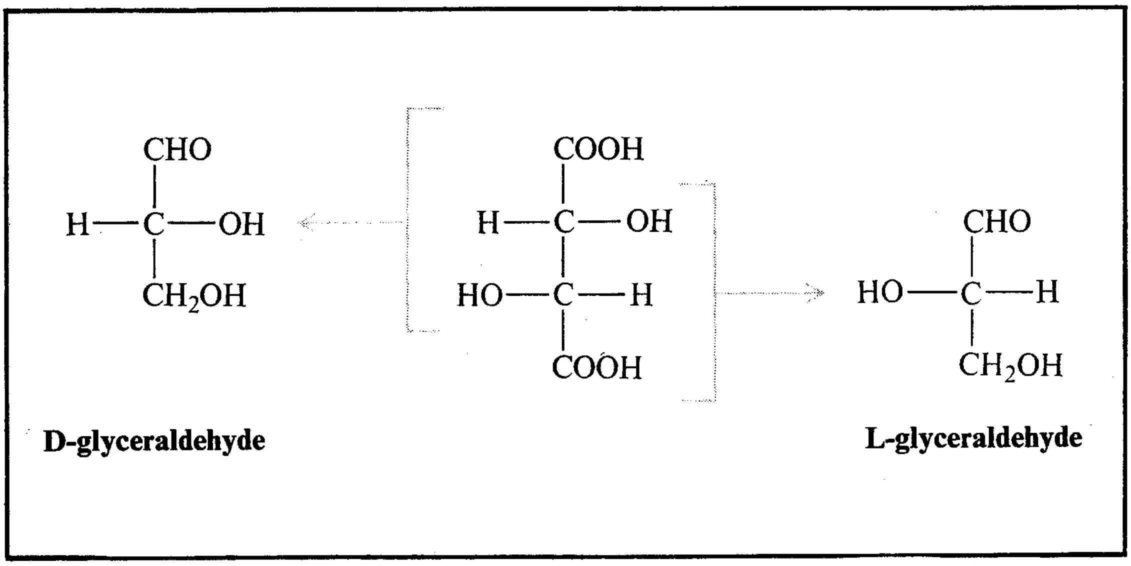

Fig. 128 Dextrorotatory tartaric acid, whose formula is shown in the centre, was called both D-tartaric acid and L-tartaric acid. Depending on the method used it can be correlated with both of the optical antipodes of glyceraldehyde. According to the new nomenclature the optical antipode represented here is called, in a completely unequivocal way, *RR*.

$I \longrightarrow Br \longrightarrow Cl \longrightarrow SO_3H \longrightarrow SCH_3 \longrightarrow SH \longrightarrow F \longrightarrow OCH_3 \longrightarrow$

$\longrightarrow OH \longrightarrow NO_2 \longrightarrow N(CH_3)_2 \longrightarrow NH_2 \longrightarrow CF_3 \longrightarrow COOCH_3 \longrightarrow$

$\longrightarrow COOH \longrightarrow CONH_2 \longrightarrow COCH_3 \longrightarrow CHO \longrightarrow CHOH{-}CH_3 \longrightarrow$

$\longrightarrow CH_2OH \longrightarrow CN \longrightarrow C_6H_5 \longrightarrow C(CH_3)_3 \longrightarrow CH(CH_3)_2 \longrightarrow C_2H_5 \longrightarrow$

$\longrightarrow CH_3 \longrightarrow Li \longrightarrow D \longrightarrow H \longrightarrow$: electron lone pair

Fig. 129 The priority of some of the most common substituents in the nomenclature of Cahn, Ingold and Prelog.

sense of the sequence L→M→S from the side opposite to the H substituent. For such a purpose the asymmetric atom may usefully be compared to the wheel of a motorcar, where the C-H bond coincides with the axle and the other bonds with the spokes. If the axle rotates so that the sequence L-M-S is clockwise, the configuration is called *R* (from *rectus*, Latin for right); on the other hand, if the sequence is anticlockwise, the configuration is called *S* (*sinister*, Latin for left) (Fig. 130). The assignment of the configuration is easily accomplished with three-dimensional models; but it can also be done by a simple examination of the Fischer projection. The rule given above can be applied directly when the substituent H is placed below or above the projection; however, the convention must be inverted if H is in a side position. This statement becomes clearer if

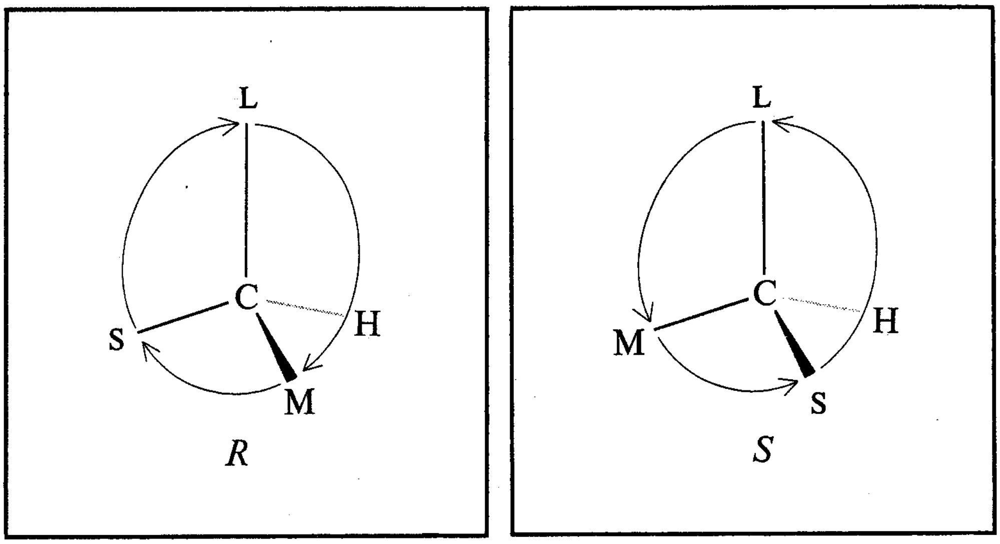

Fig. 130 The method of observing a tetrahedral atom and the assignment of its configuration.

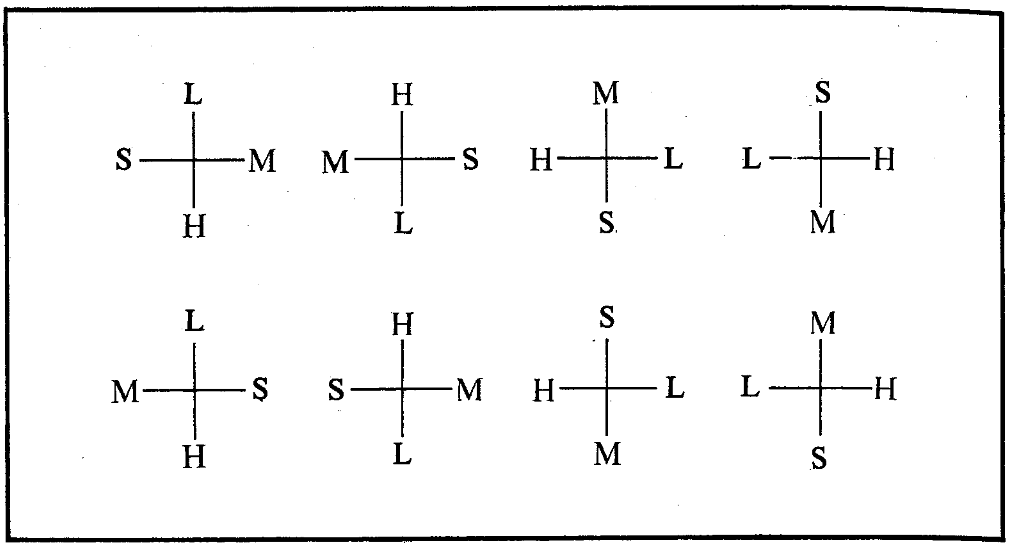

Fig. 131 Assignments of configuration from Fischer projections. The *R* enantiomorph is shown above and the *S* below. The first two formulae of each line have the smallest substituent (H) above or below. The rule is thus applied in its normal form (if the sequence L→M→S is dextrorotatory the configuration is *R*). In the remaining formulae with H at the side, the rule must be inverted. The different Fischer projections of the same optical antipode are obtained by making two exchanges of the substituents.

one remembers that the horizontal bonds in the Fischer projection come out above the paper while the vertical ones come out below and that, consequently, the formulae can be rotated through 180° around an axis perpendicular to the paper without the configuration being altered. On the other hand, a rotation of 90°, or the exchange of any two substituents, converts a compound into its optical antipode. Obviously, if two, or in general an even number, of exhanges of substituents are involved, the new projection is identical to the first. Figure 131 shows some examples of configurational determinations using Fischer projections.

The nomenclature of Cahn, Ingold and Prelog can also be applied to allenes, spirans and the other cases of dissymmetric compounds not containing asymmetric atoms. Being based on topological considerations it is of universal and absolutely unequivocal use. Yet even this is open to an unavoidable criticism.

The sense of the configuration (*R* or *S*) is related to the ordering of substituents according to purely formal rules, with the result that similar compounds can belong to opposite series even if they have configurations which appear intuitively equal; or in substitution reactions there can be a change from *R* to *S* without an inversion of configuration and *vice versa* (Fig. 132). In spite of these marginal difficulties, the *RS* nomenclature has the merit of having made configurational notation completely unequivocal (for example, dextrorotatory tartaric acid, whose ambiguous correlation with glyceraldehyde was previously discussed, is *RR*) and allows the absolute configuration of any stereoisomer to be given immediately, freeing it from any reference to other compounds.

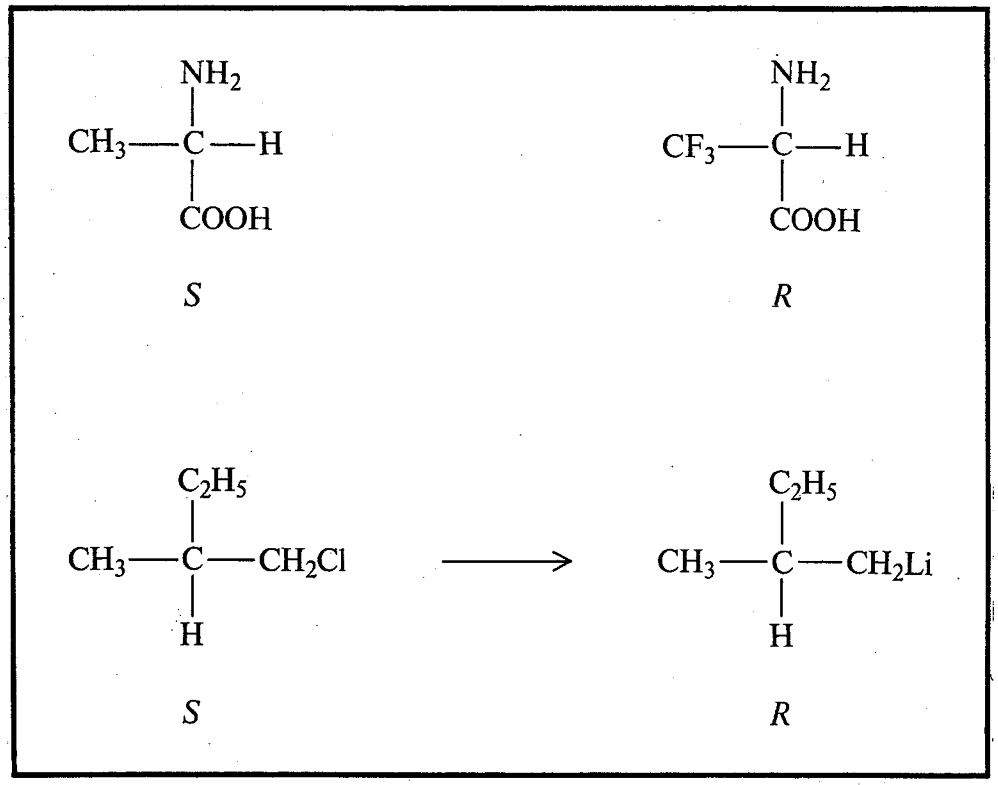

Fig. 132 The two amino acids represented above belong to the same steric series; but their names are opposite because of the different priority of the substituents. Below: the reaction between *iso*amyl chloride (*S*) and lithium does not alter the configuration of the asymmetric atom but the new compound has the *R* configuration. The order of precedence of the substituents is as following: $CH_2Cl > C_2H_5 > CH_2Li > CH_3 > H$

Appendix III

Symmetry elements and groups

The symmetry elements defined in the text on page 94 may be indicated by a symbolic notation which makes the treatment clearer. Simple axes of rotation are indicated by C_n (n being the order of the axis), alternating or rotation-reflection axes by S_n, symmetry planes by σ (or S_1) and a centre of symmetry by i (or S_2). The symbols σ_h and σ_v indicate that the symmetry plane is horizontal or vertical when the object is placed in such a way that the rotation axis of highest order (principal axis) is vertical.

The set of symmetry operations which can be carried out on a certain object constitutes a symmetry group. Without entering into a detailed discussion of group theory, we can say that any group is distinguished by a particular type of symmetry and that knowledge of the group to which it belongs immediately allows all the symmetry properties of a particular body to be known. We shall use the Schoenflies notation to indicate the different groups. For simplicity we shall give the symmetry elements of each group and not the possible operations which lead to them.

A molecular structure (or any other structure) is said to belong to the $\mathbf{C}_1$ group if it does not possess any symmetry elements except for the rotation axis of order I: $\mathbf{C}_1 = C_1$; it belongs to the $\mathbf{C}_s$ group if it has a symmetry plane $\mathbf{C}_s=\sigma$ (or S_1); it belongs to the $\mathbf{C}_i$ group if it contains only a centre of inversion or symmetry $\mathbf{C}_i = i$ (or S_2).

In contrast to these, other groups have one (and only one) rotation axis or order greater than 1. They are: the group $\mathbf{S}_n$ (n equal to or greater than 2) with an alternating axis of order n; the group $\mathbf{C}_n$ (n greater than 1) with a simple rotation axis of order n; the group $\mathbf{C}_{nv}$ which has a rotation axis of order n and n symmetry planes containing the rotation axis (σ_v); the group $\mathbf{C}_{nh}$ with a rotation axis of order n and a plane of symmetry perpendicular to the axis (σ_h).

A third type of symmetry groups, indicated by the letter **D** (abbreviation of dihedral), contains two types of symmetry axes: one, called the principal axis and placed vertically, of order n (C_n) and

Table VIII. Some of the more important symmetry groups

	CHIRAL GROUPS		
$\mathbf{C}_1$	$= C_1$ (no element)*	$\mathbf{C}_1$	= a hand
$\mathbf{C}_n$	$= C_n$	$\mathbf{C}_2$	= a pair of scissors, a spring
$\mathbf{D}_n$	$= C_n + nC_2$	$\mathbf{D}_3$	= a propeller with three blades
	NON-CHIRAL OR NON-DISSYMMETRIC GROUPS		
$\mathbf{C}_s$	$= \sigma\,(S_1)$	$\mathbf{C}_s$	= a spoon
$\mathbf{C}_i$	$= i\,(S_2)$	$\mathbf{C}_i$	= a photographic projector (in particular, the system; object, lens and image)
$\mathbf{S}_n$	$= S_n$ (n even)	$\mathbf{S}_n$	= a bicycle wheel
$\mathbf{C}_{nv}$	$= C_n + n\sigma_v$	$\mathbf{C}_{4v}$	= a pyramid
		$\mathbf{C}_{\infty v}$	= a cone
$\mathbf{C}_{nh}$	$= C_n + \sigma_h$	$\mathbf{C}_{2h}$	= the letters N, S, Z
$\mathbf{D}_{nh}$	$= C_n + nC_2 + \sigma_h + n\sigma_v$	$\mathbf{D}_{6h}$	= a new pencil (not sharpened)
		$\mathbf{D}_{\infty h}$	= a cylinder
$\mathbf{D}_{nd}$	$= C_n + nC_2 + n\sigma_d$	$\mathbf{D}_{2d}$	= a tennis ball
$\mathbf{T}_d$	$= 4C_3 + 3C_2 + 6\sigma$	$\mathbf{T}_d$	= a tetrahedron
$\mathbf{O}_h$	$= 3C_4 + 4C_3 + 6C_2 + 9\sigma$	$\mathbf{O}_h$	= a cube
$\mathbf{K}_h$	= all possible elements	$\mathbf{K}_h$	= a sphere

* More exactly this group should be called asymmetric.

n binary axes perpendicular to this. The groups $\mathbf{D}_n$ contain only symmetry axes ($\mathbf{D}_n = C_n + nC_2$); the groups $\mathbf{D}_{nh}$ contain also a horizontal plane of symmetry (σ_h) and n vertical planes of symmetry (σ_v); the $\mathbf{D}_{nd}$ groups, contain the axes and n vertical planes called σ_d (so they do not contain the binary axes; d is for diagonal). Increasing the degree of symmetry, we have the groups with axes of order greater than 2. Those with the most stereochemical interest are the tetrahedral group $\mathbf{T}_d$, the octahedral group $\mathbf{O}_h$ and, finally, that of the sphere $\mathbf{K}_h$. This last group contains all the possible elements of symmetry.

With regard to the possibility of enantiomorphism (see the text on page 99), it is useful to divide the symmetry groups into two classes, those without mirror symmetry (chiral groups) and those with mirror symmetry. It is possible to discriminate between the two classes by seeing whether or not there are alternating axes of any order (S_n and, in particular, σ and i, a plane and centre of symmetry).

In Table VIII we give the list of the most common groups, the symmetry elements which characterize them and some non-chemical examples chosen from normal objects.

Some molecular structures belonging to various symmetry groups are represented in the drawings in the text on pages 100–103.

Bibliography

We suggest the following books to the reader who wishes to broaden his knowledge of stereochemistry.

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ELIEL, ERNEST L., ALLINGER, NORMAN L., ANGYAL, STEPHEN J., and MORRISON, GEORGE A., *Conformational Analysis,* New York, Interscience, 1965.

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Topics in Stereochemistry (Vols. I to V), New York, Interscience (1967 onwards).

Index

A LONGMAN

TEXT

STEREOCHEMISTRY
Natta and Farina

A clear and interesting introduction to stereochemistry for undergraduate students of chemistry, biochemistry and biology, well supported by many two-colour diagrams.

The influence of the spatial arrangement of atoms in a molecule upon the reactivity of that molecule has been found to be of major importance. To understand the relationship between structure and reaction it is necessary to turn to stereochemistry, to think in three-dimensional terms. The importance of stereochemistry in chemistry, biochemistry, molecular biology and the polymer industries is considerable. As greater knowledge of the details of the mechanism of chemical reactions is obtained so the importance of stereochemistry is seen to increase.

After a short historical introduction the authors give a short résumé of the theory of atomic and molecular structure as a basis for a discussion of molecular symmetry and optical activity. This is followed by an account of the effects of stereochemistry on reactivity. Next polymers are considered, both synthetic and biological—and the relation between molecular structure and physical properties discussed. An account of the stereochemical basis of protein synthesis in the cell is given together with accounts of the mechanisms proposed for other natural processes—drug action, enzyme action, and vision. The book concludes with a speculative account of the possible origin of natural activity. Appendices deal with the nomenclature and mathematics in more detail, with an interesting sidelight upon the early history of stereochemical theory.

Giulio Natta, who won the Nobel Prize for chemistry in 1963, is the director of the Institute for Industrial Chemistry at Milan Polytechnic and president of the National Centre for Macromolecular Chemistry of the National Research Council of Italy.

Mario Farina has collaborated for more than fifteen years with Professor Natta at Milan Polytechnic. He is the author of over 100 scientific publications mostly concerned with problems of organic and macromolecular stereochemistry.

Andrew Dempster, M.Sc., Ph.D. (the translator), is Lecturer in Molecular Spectroscopy, [illegible] University, Ankara, Turkey.

The front cover shows a photograph by Paul Brierley of a large-scale model of a polypropylene molecule on display at the Philips Evoluon exhibition at Eindhoven, Holland. Much of the original work on the synthesis and structure of polypropylene was carried out by Giulio Natta at the Milan Polytechnic—see pages [illegible]