# A FRAGMENT OF STEREOCHEMISTRY

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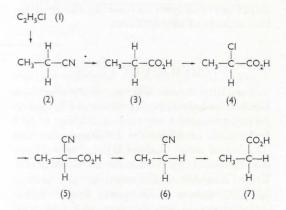
This article provides only a part of the nomenclature of stereochemistry and completely ignores the historical development of the subject. Instead, it indicates the type of information on which our ideas concerning stereochemistry are based

THE TETRAHEDRAL DISTRIBUTION OF BONDS

Qualitative analyses followed by quantitative analyses and molecular-weight determinations allow us to assign molecular formulae to organic compounds. Every organic compound has a distinct set of physical and chemical properties which differentiates it from every other compound. The physical properties most frequently used in this work include the melting point. the boiling point and interactions with light and other electromagnetic radiations. These interactions are exemplified by the refraction and absorption of light, the absorption of infra-red and ultra-violet radiation, and the rotation of the plane of plane-polarized Data of the type outlined above light. enable us to say, without fear of contradiction, that whereas, for example, there are two compounds with the molecular formula C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>, each of the formulae CH<sub>4</sub>, C<sub>2</sub>H<sub>6</sub> and C<sub>2</sub>H<sub>5</sub>Cl represents only one compound. The action of potassium cyanide on ethyl chloride (1) gives propionitrile (2) from which propionic acid (3) can be obtained by hydrolysis. The action of chlorine on this acid can give 2-chloropropionic acid (4) which, by interaction with potassium cyanide, gives 2-cvanopropionic acid (5). This compound, at sufficiently raised temperatures, evolves carbon dioxide and leaves us with propionitrile (6) which is identical in every respect with propionitrile (2) and hydrolyses to propionic acid (7) which is identical with propionic acid (3). This series of reactions does not provide us with a straight (3) and a bent (7) type of propionic acid as it could have done had the four valencies of carbon been directed towards the corners of a square.

The hydrolysis of 2-chloropropionic acid (4) gives lactic acid, CH<sub>3</sub>·CH(OH)·CO<sub>2</sub>H, and if

we proceed to prepare a number of its salts and study their recrystallization from water. we shall find, sooner or later, that the crystals provided by a particular salt are of two types, both asymmetric (since should Alice retrieve the image of any one crystal from behind the mirror it would not be superimposable on the crystal in front of the mirror) and related to one another as object to mirror image. Given great patience, good eyesight and a steady hand we can separate the crystals of one type from those of the other and thereafter recover separately the lactic acid from each. The two samples of lactic acid thus obtained have identical physical properties except in their effect on plane-polarized light. Both are optically active: one, named (+)-lactic acid. rotates the plane of polarization clockwise (relative to the observer) while the other, (-)-lactic acid, rotates it to exactly the same extent but anticlockwise. The ability to rotate the plane of polarized light is not lost

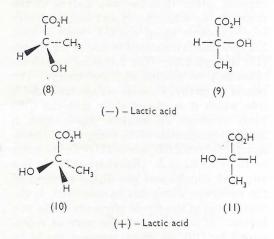


when the two lactic acids are in solution: we conclude, therefore, that the molecules of lactic acid are asymmetric, a molecule of (-)-lactic acid being the mirror image of a molecule of

(+)-lactic acid. That compounds of the type Ca<sub>4</sub>, Ca<sub>3</sub>b and Ca<sub>2</sub>bc are unique while those, like lactic acid, of the type Cabcd can occur in (+)- and (-)-forms finds its interpretation in the concept that the bonds attaching a carbon atom to four other atoms are directed from the centre to the four corners of a regular tetrahedron.

#### CONFIGURATION

An attempt to give a three-dimensional representation of the two forms of lactic acid is shown below (8 and 10). Fischer projections provide a convenient form of threedimensional representation (9 and 11 are the Fischer projections of 8 and 10). To obtain them, project on to the paper what an eye would see if, as it looks at the central carbon atom, the bonds directed *away from* the observer are in a *vertical plane* while those directed *towards* the observer are in a *horizontal plane*.

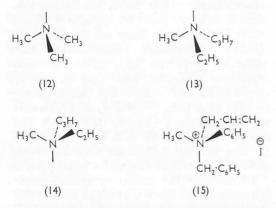


When, as in lactic acid, four different atoms or groups of atoms are attached to the same carbon atom, this atom is called an *asymmetric carbon atom*, since there are two arrangements or *configurations* of the atoms and groups attached to it. Pairs of molecules that are non-superimposable and are the mirror image of each other are called *enantiomers, enantiomorphs,* or *optical isomers.* When enantiomers are present in equal amount, the whole is optically inactive and is called a *racemate.* The lactic acid we prepared from propionic acid by chlorination followed by hydrolysis is optically inactive and is called racemic or (+)-lactic acid.

Living organisms usually produce only one enantiomer of a pair; thus the vegetable kingdom provides many optically active nitrogenous organic bases. When one of these bases, e.g. (-)-quinine from the bark of the cinchona tree, reacts with (+)-lactic acid, two salts are formed which can be represented by (-)-B,(+)-A and (-)-B,(-)-A in which A and B represent the acid and the base respectively. These two salts are not enantiomeric: they have the same configuration in one part and opposite configurations in the other. They are diastereomeric. enantiomers, diastereomers have Unlike different properties and, often, are conveniently separated from one another by Thus we can separate recrystallization. (-)-B,(+)-A from (-)-B,(-)-A; afterwards we can obtain (+)-lactic acid from the former and (-)-lactic acid from the latter. In this manner (+)-lactic acid has been resolved into its optically active enantiomers.

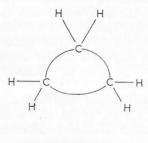
To discover the actual or absolute configuration of the lactic acid which rotates the plane of polarized light to the right and of that which rotates it to the left, we must, sooner or later, directly or indirectly, have recourse to X-ray diffraction patterns from which we can precisely deduce the spatial arrangement of the parts of a molecule. Formulae 8 and 9 represent (-)-lactic acid and formulae 10 and 11 (+)-lactic acid. The esterification of (-)-lactic acid with methyl alcohol gives the (+)-methyl ester in which the -CO<sub>2</sub>CH<sub>2</sub> group occupies the same relative position in the molecule as does the -CO<sub>2</sub>H group in the molecule of (-)-lactic acid. Thus we are compelled to recognize that two compounds may have similar configurations yet rotate the plane of polarized light in opposite directions.

Is the 'tetrahedral distribution' of bonds shown by carbon atoms also a feature of atoms of other elements? Electron-diffraction data concerning trimethylamine (12) have shown the molecules to be pyramidal with  $C^{N}C$  angles of about 108°, very nearly the same as the  $H^{C}H$  angles  $(109.5^{\circ})$  of methane molecules. We might expect to find optically active forms (13) and (14) of methylethylpropylamine, but optical isomers of this kind have not been found. Spectroscopic data show that the pyramidal molecules (13) and (14) require only about 5 kcal/mole to enable the pair of unshared electrons to pass through the nitrogen atom and thereby invert the configuration. This amount of energy is readily available at room temperature. When the four pairs of electrons surrounding the nitrogen atom are



used to bond the nitrogen atom to four different groups, as in methylallylphenylbenzylammonium iodide (15), two optically active forms exist. Clearly, the carbon atom is not the only one which can have its bonds directed from the centre to the corners of a regular tetrahedron, the angle between any two bonds being about  $110^{\circ}$ .

When 1,3-dichloropropane is allowed to react with zinc, cyclopropane (16) is formed.



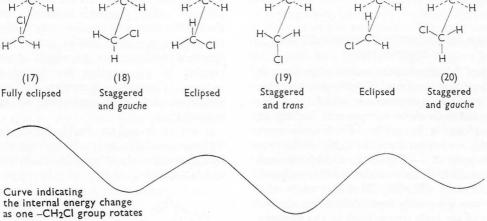
(16)

What has happened to the interbond angle of  $110^{\circ}$ ? Perhaps we ought to conclude that bonds can be bent into the sausage shape shown in formula (16). From our knowledge

of the molecular shapes of many compounds and of the energy, measured by infra-red spectroscopy, to change intramolecular vibrations, we are able to deduce that bonds are easier to bend than to stretch.

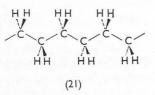
#### CONFORMATION

When we construct a model of a molecule of ethylene chloride we find that, without stretching or bending bonds, we can obtain a variety of molecular shapes by rotating one half of the molecule relative to the other half about the bond joining the carbon atoms. Nearly aligning our eyes with the C-C bond, let us begin with the chlorine atoms and hydrogen atoms eclipsing one another as shown in (17) and gradually rotate the nearer -Higu group so +but we pass +burvage +bre shapes represented by (18), (19) and (20). Since no one has found two or more types of ethylene chloride, we might be led to suppose either that the two halves of the molecule can rotate freely and independently of one another about the C-C bond or that the molecule is restricted to one of the shapes (17) through (20). The following considerations help to resolve this ambiguity. The effects of methyl chloride on electrical fields into which it is placed show that the C-Cl bond provides an electric dipole with a moment (magnitude of the charges  $\times$  distance apart) of about 2.0D, where 1D or Debye units  $= 10^{-11}$  e.s.u.  $\times$  Å. Ethylene chloride has two such dipoles and the dipole moment of the molecule, which can be measured, is the vector sum of the dipole moments of the two halves. If ethylene chloride were as represented by (19), its dipole moment would be zero; if as represented by (17), 3.8D. Free rotation would provide the average value of  $(0+3\cdot8)/2 = 1\cdot9D$ . Experiment reveals that its dipole moment is 1.12D at  $32^{\circ}$  and gradually increases with rise in temperature until it is 1.54D at 271°. The data are compatible with the view, now generally held, that, as one half of the molecule rotates with respect to the other (a) the internal energy of the molecule rises and falls as shown by the curve under formulae (17) through (20), (b)the molecule can rest only in the energy hollows, (c) the molecule prefers the hollow provided by (19) to the shallower hollows provided by (18) and (20) and (d) this preference becomes less apparent as the temperature is raised. The various molecular



shapes (17) through (20) are called *conforma*tions; (19) shows the molecule in its trans conformation while (18) and (20) show the molecule in its gauche or skew conformations. In each of these conformations, the bonds radiating from one carbon atom are staggered with respect to those radiating from the other.

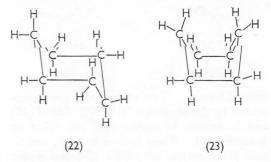
X-ray diffraction patterns produced by paraffin wax show the polymethylene chains to have the zig-zag conformation (21) in



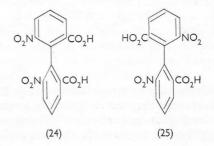
which every group of four consecutive methylene groups has the staggered and *trans* conformation.

When we construct a model of the cyclohexane molecule, only two conformations are possible if we are to have an interbond angle of  $110^{\circ}$ : the *chair* conformation (22) and the *boat* conformation (23). The infra-red spectrum of cyclohexane shows that at ordinary temperatures the molecules spend a much longer time in the chair than in the boat conformation. Only in the former are the when more important demands on shape are absent. It may originate in repulsive forces between atoms and groups, especially the bulkier ones, which are brought close together without being able to bond one to the other.

bonds of each carbon atom staggered with



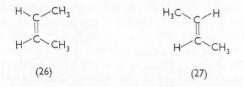
The resolution of 6,6'-dinitrodiphenic acid into its optical isomers (24) and (25) demonstrates that in this compound an amount of



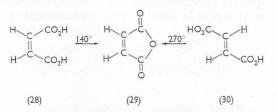
energy too large to be readily available at ordinary temperatures is required to enable the substituents in one of the rings to squeeze past those in the other. It is noteworthy that the non-planar molecules (24) and (25) are asymmetric although they do not contain an asymmetric atom.

## THE COPLANARITY REQUIREMENT OF DOUBLE BONDS

When 2-bromobutane reacts with bases it can lose the elements of hydrogen bromide and give a hydrocarbon which can be separated into three components boiling at  $-6^{\circ}$ ,  $1^{\circ}$  and  $4^{\circ}$  severally. Each component has the molecular formula  $C_4H_8$ . The one which boils at  $-6^{\circ}$  gives formaldehyde and propionaldehyde on ozonolysis and is assigned "bne fromulna (H13; H12; H12; "wilne "bne other two give only acetaldehyde on ozonolysis and are both represented by the formula CH<sub>3</sub>·CH:CH·CH<sub>3</sub>. Of these two hydrocarbons, the one with the higher boiling point has a dipole moment and the other has not; consequently, they are given respectively the formulae (26) and (27) and named cis- and

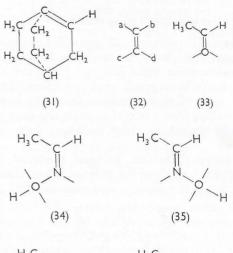


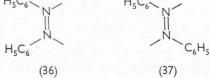
trans-2-butene. Two compounds are represented by the structure  $HO_2C \cdot CH : CH \cdot CO_2H$ ; one is known as maleic and the other as fumaric acid. When heated to 140°, maleic acid gives maleic anhydride (29) and water while fumaric acid loses water to form maleic



anhydride only at temperatures above 270°; consequently, they are assigned the formulae (28) and (30) respectively. Clearly, the energy barrier to rotation about a carboncarbon double bond is sufficiently high to hold the four attached atoms or groups in a rigid configuration except at high temperatures. Electron diffraction and spectroscopic studies show ethylene to be a flat molecule with bond angles of about  $120^{\circ}$ . The isomers (26) and (27) and again (28) and (30) are called *geometric* isomers. Isomers that differ from one another only in the way the atoms are oriented in space but are identical with respect to which atoms are bonded to one another are called *stereoisomers*. Geometric isomerism and optical isomerism are both examples of stereoisomerism.

A carbon-to-carbon double bond requires coplanarity of the two carbon atoms and the four atoms directly attached to them (see 32); understandably, olefins of the type (31)

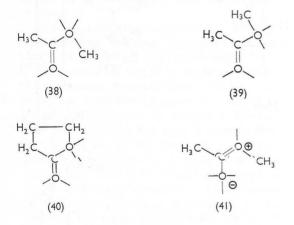




cannot be obtained. Now let us turn our attention briefly to double bonds between atoms other than two carbon atoms. Although there is only one type of acetaldehyde (*see* 33), this compound condenses with hydroxylamine to give two oximes, (34) and (35). Further, *cis*- and *trans*-forms of azobenzene, (36) and (37), are well known. In the formulae (33) through (37) unshared pairs of electrons, like shared pairs, are represented by lines. Clearly, a double bond between atoms imposes planarity even when the two atoms are other than carbon atoms, and is capable of providing geometric isomers when between carbon and nitrogen atoms or between two carbon or two nitrogen atoms.

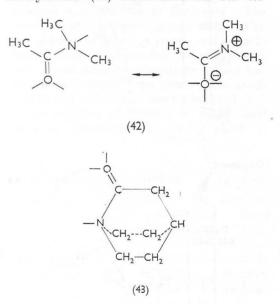
#### CONJUGATION AND CONFORMATION

To what extent does the planarity required by a double bond determine the shape of an ester molecule? If the bonding in methyl acetate is correctly represented by (38), only the methyl group attached to an oxygen atom is free to move out of the plane of the rest of the molecule. Perhaps it is free to rotate about the bond joining its oxygen atom to the carbonyl group. The wholly planar conformations (38) and (39) represent the molecule in its least polar and most polar



forms respectively. Conformation (39) should provide a dipole moment of about 4.0D, since this is the moment of  $\gamma$ -butyrolactone (40). Calculation leads us to expect conformation (38) to provide a moment of 1.5D. Free rotation of the methyl group through these two extreme conformations would provide an average moment of 2.7D. The measured value is 1.7D and does not change as the temperature of the ester is raised.

We must conclude that methyl acetate is firmly held to conformation (38). The popular interpretation of this conclusion is based on the concept that a pair of electrons, shown in (38) as belonging only to the oxygen atom of the methoxyl group, reaches to some extent into the carbon atom of the carbonvl group. This electronic redistribution, taken to 100 per cent, would result in structure (41); developed to the extent of only 10-15 per cent it would provide partial double bonding between methoxyl and carbonyl groups sufficient to require the methyl group of the methoxyl group to be near the plane of the rest of the molecule. This interpretation does not discriminate between conformations (38) and (39): perhaps dipole-dipole interaction of methoxyl and carbonyl groups gives preference to (38). The partial double bonding introduced above is referred to as conjugation or electron delocalization. It lowers the internal energy of any molecule in which it occurs and may require a degree of molecular planarity which is not apparent from the usual formulation. Should we fail to recognize that a molecule like acetdimethylamide (42) must have all but its



hydrogen atoms close to one plane if nitrogen atom and carbonyl group are to be conjugated, we would wonder why, despite the efforts of some of the world's best chemists, the compound to be assigned the formula (43) has not been prepared (cf. 31).

So far, this article has included very little chemistry, since it is concerned only with the shapes of molecules—a topic which these days requires no chemistry. Chemistry is concerned with processes in which bonds are changed, some being broken, others being made, and we must direct our attention to the shape requirements of some of these processes if the word 'stereochemistry' is to appear in the title of this article.

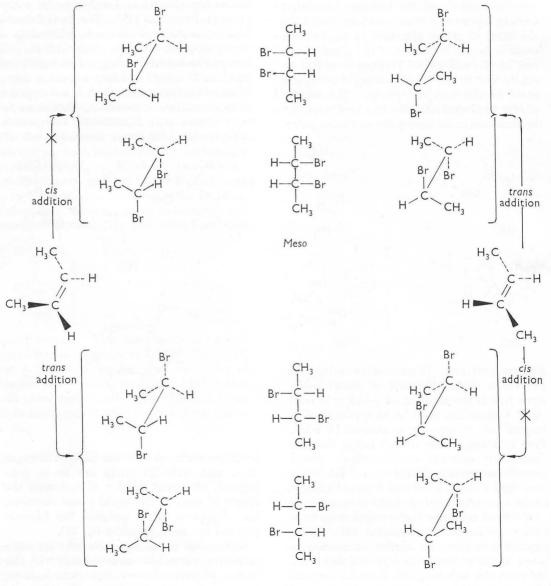
### ADDITIONS TO ETHYLENIC DOUBLE BONDS

Bromine rapidly adds on to ethylene to give ethylene bromide, from which ethylene

can be regenerated through the agency of zinc:

$$\operatorname{CH}_2: \operatorname{CH}_2 + \operatorname{Br}_2 \to \operatorname{CH}_2 \operatorname{Br} \cdot \operatorname{CH}_2 \operatorname{Br} \to \operatorname{CH}_2: \operatorname{CH}_2$$

Similarly, both cis- and trans-2-butene combine rapidly with bromine to give 2,3-dibromobutane, and if zinc is allowed to react with these two samples of dibromobutane, that from cis-2-butene regenerates cis-2butene while that from trans-2-butene

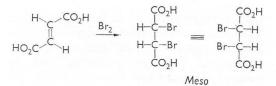


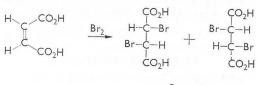
Racemic

regenerates trans-2-butene. Thus we are driven to the surprising though unavoidable conclusion that the 2,3-dibromobutane from cis-2-butene is different from that from trans-2-butene. The accompanying chart shows all possible addition products of bromine with cis- and trans-2-butene. Each of the four formulae down the centre of the chart is the Fischer projection of the three-dimensional formulae which flank it. Molecular models save us much mental juggling when we try to assure ourselves that any three formulae of 2.3-dibromobutane which are side by side can be interconverted merely by rotating one half of the molecule with respect to the other half, and that all three formulae therefore represent the same molecule in different conformations. Do the four rows of formulae represent four different molecules? There are several ways of finding the answer. Let us find it by considering only the Fischer projections.

All four projections look different: do they represent four different molecules? If we turn over the lowest one, as we might turn over a hand from the palm-up to the palmdown position, it would then look like the projection immediately above it. But if a Fischer projection is to remain a Fischer projection we must not turn it over in this way, for if we do the bonds in a vertical plane will no longer be directed away from us and the bonds in horizontal planes will no longer be directed towards us. All we can do to a Fischer projection is rotate it in the plane of the paper through 180°. If we do this to the bottom two projections each retains its identity: they represent two If we slide between different molecules. them a mirror which is perpendicular to the plane of the paper we see that each is the mirror image of the other: they are optical isomers. Whether they are formed by transaddition of bromine to cis-2-butene or cisaddition of bromine to trans-2-butene, they will be formed in equal amount: that is. racemic 2,3-dibromobutane will be formed. When we rotate the topmost projection through 180° it becomes the second one down: the top two projections represent the same molecule. When we place a mirror alongside these two projections we see that each is the mirror image of the other: therefore, they represent a molecule which is not asymmetric and cannot be optically active, even though it contains two asymmetric carbon atoms. They represent meso 2,3-dibromobutane. In the meso form, both halves of the molecule are asymmetric and, as shown by a vertical mirror so placed as to bisect either of its projection formulae, one half of the molecule is the mirror image of the other half. We see that 2.3-dibromobutane can occur in two optically inactive forms: the racemic form which is a mixture of equal parts of (+)- and (-)-2,3-dibromobutane, and the meso form in which all the molecules are identical and optically inactive. Meso and racemic forms are diastereomeric, since if we compare a molecule of the former with a molecule of either enantiomer of the latter we shall find the two molecules have the same configuration in one half of their molecules and opposite configurations in the other. The two different 2,3-dibromobutanes obtained by the addition of bromine to cis- and trans-2butene must be the racemic and meso forms. but not necessarily respectively. How can we discover which form comes from cis-2butene and which from trans-2-butene?

The addition of bromine to maleic acid gives a dibromosuccinic acid which is





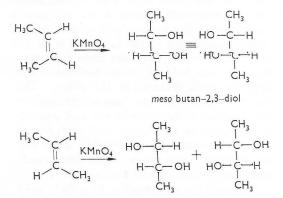
Racemic

different from the one obtained by the addition of bromine to fumaric acid. Remembering how we resolved  $(\pm)$ -lactic acid with the aid of an optically active base, let us try to resolve these two dibromosuccinic acids.

Success crowns our efforts only when we work on the one from maleic acid. Thus we

learn that maleic acid gives *racemic* dibromosuccinic acid and that the *meso* dibromo acid is obtained from fumaric acid. If we are persuaded by analogy, we shall expect the addition of bromine to *cis-* and *trans-2*butene to give *racemic* and *meso* 2,3-dibromobutane respectively. We see that the addition of bromine across an ethylenic double bond is orderly: *stereospecific* is the adjective which best describes it. The reaction is a *trans-*addition.

Another chemical property of olefins is their ability to decolorize permanganate. A glycol is formed in this reaction, a hydroxyl group having been added to each of the two

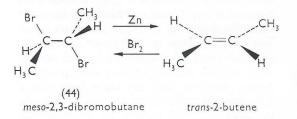


racemic butan-2,3-diol

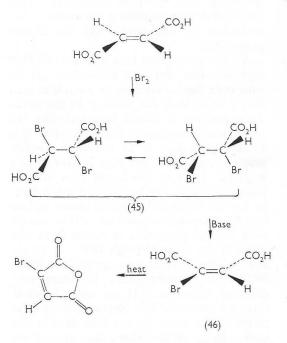
carbon atoms involved in the double bond. The permanganate oxidation of *cis*- and *trans*-2-butene provides two different glycols: only the glycol from *trans*-2-butene can be resolved (I wonder how it was resolved). No doubt the reaction of olefins with permanganate leads to the *cis*-addition of two hydroxyl groups.

### ELIMINATION REACTIONS

Although molecules of *meso-2,3*-dibromobutane can turn from one conformation to another, one half of each molecule being able to rotate with respect to the other half, this compound reacts with zine to give *trans-* and not *cis-2*-butene. Apparently, in this elimination process the molecule is required to have the conformation in which the bromine atoms are most widely separated: that is, the conformation in which the two bromine atoms and the two carbon atoms that link them are all in one plane and the bromine atoms are on opposite sides of the bond joining the two carbon atoms. This requirement is represented by formula (44). The reaction is



stereospecific and is suitably described as a *trans*-elimination. This stereospecificity allows the reaction of *racemic* 2,3-dibromobutane with zinc to give only *cis*-2-butene.



Molecules which have a hydrogen atom and a halogen atom attached to adjacent carbon atoms can react with base so as to lose the elements of hydrogen halide and acquire an additional bond between the two carbon atoms. What is the stereochemistry of this elimination process?

Having already obtained *meso* dibromosuccinic acid (45) by the addition of bromine to fumaric acid, let us now, through the agency of a base, remove from it the elements of hydrogen bromide. The product readily forms an anhydride and is therefore bromomaleic acid (46).

Similarly, *racemic* dibromosuccinic acid, which we obtained by the addition of bromine to maleic acid, gives bromofumaric acid. These reactions are *trans*-eliminations: they require the hydrogen and bromine atoms which are to be eliminated and the two carbon atoms which link them to be in one plane, and the hydrogen and bromine atoms to be on opposite sides of the bond joining the two carbon atoms.

Stereochemistry is concerned with the geometry of chemical reactions, and it helps

# THE SCIENCE MUSEUM

The chemistry section of the Science Museum, London, has been completely revised and greatly enlarged to occupy an area of  $10,000 \text{ ft}^2$  divided into three galleries. The development of the new section has been supported by a contribution of £30,000 from the chemical industry, and the Scientific Instrument Manufacturers' Association have lent several items of modern equipment.

One gallery is concerned with chemical constitution. It contains a large illuminated Periodic Table of the elements designed to show the history of our knowledge of the elements and is operated by push buttons. An important section of this gallery shows the discovery and uses of X-ray crystallography.

The second gallery concentrates on the chemistry of the world around us, particularly the composition of the atmosphere. The subject of geochemistry is introduced here with exhibits showing the composition of the earth and some of the prospecting methods used for economic exploitation.

The third gallery is devoted to the practical methods of chemistry which it traces from the beginning of chemistry to the present day. There is a series of full-scale and miniature laboratories, including a reproduction of a 16th century assayer's laboratory and a reconstruction of the working conditions of the Government Chemist's Laboratory of 1895. Modern techniques are shown in two us tremendously in our attempts to discover their mechanisms. The elucidation of the mechanisms of reactions not only satisfies our curiosity; it helps us to foretell the practical procedure most likely to bring about a required reaction. Although there are numerous reactions, there are but few tupes of reaction, each defined by its stereochemistry and mechanism. The fragment of stereochemistry provided by this article is concerned with the geometry of one or two addition and elimination processes; I hope we are ready and anxious to discover the stereochemistry of other types of reactions, especially that of substitution processes, since they make a vast contribution to chemistry.

modern laboratory rooms, one of which displays routine operations, the other being used for special exhibitions.

The new section is designed to provide facilities for displaying new developments and to allow parties of students to obtain maximum benefit from the exhibits.

## CHEMICAL EDUCATION AWARD

Dr Christian Sivertz, retired associate professor of chemistry, University of Western Ontario, has been named to receive the Chemical Education Award of the Chemical Institute of Canada.

Born in Point Roberts, Washington in 1897, Dr Sivertz graduated as a chemical engineer from the University of British Columbia, Vancouver, and received his M.Sc. and Ph.D. in chemistry from McGill University, Montreal in 1926; he then joined the faculty of the University of Western Ontario from which he retired last year.

Dr Sivertz was an active participant in the Canadian High Polymer Forum and he served on the National Research Council Associate Committee on Synthetic Rubber Research. He is a Fellow of the Chemical Institute and served on its Council.

Dr Sivertz's lecture at the Annual Conference of the Chemical Institute of Canada this year was on the Problem of Science Education in the New Age.