CHAPTER I

PHYSICAL PROPERTIES AND CHEMICAL CONSTITUTION

§1. Introduction. A tremendous amount of work has been and is being done to elucidate the relationships between physical properties and chemical structure. An ideal state to be achieved is one where the chemist can predict with great accuracy the physical properties of an organic compound whose structure is known, or formulate the correct structure of an organic compound from a detailed knowledge of its physical properties. A great deal of progress has been made in this direction as is readily perceived by examining the methods of elucidating structures of organic compounds over the last few decades. In the early work, the structure of an organic compound was solved by purely chemical means. These are, briefly:

(i) Qualitative analysis.
(ii) Quantitative analysis, which leads to the empirical formula.
(iii) Determination of the molecular weight, which leads to the molecular formula.
(iv) If the molecule is relatively simple, the various possible structures are written down (based on the valency of carbon being four, that of hydrogen one, oxygen two, etc.). Then the reactions of the compound are studied, and the structure which best fits the facts is chosen. In those cases where the molecules are not relatively simple, the compounds are examined by specific tests to ascertain the nature of the various groups present (see, *e.g.*, alkaloids, §4. XIV). The compounds are also degraded and the smaller fragments examined. By this means it is possible to suggest a tentative structure.
(v) The final stage for elucidation of structure is synthesis, and in general, the larger the number of syntheses of a compound by *different* routes, the more reliable will be the structure assigned to that compound.

In recent years, chemists are making increasing use of physical properties, in addition to purely chemical methods, to ascertain the structures of new compounds. Furthermore, information on structure has been obtained from physical measurements where such information could not have been obtained by chemical methods. The early chemists identified pure compounds by physical characteristics such as boiling point, melting point, refractive index; nowadays many other physical properties are also used to characterise pure compounds.

The following account describes a number of relationships between physical properties and chemical constitution, and their application to the problem of elucidating chemical structure.

§2. Van der Waals forces. Ostwald (1910) classified physical properties as **additive** (these properties depend only on the nature and number of atoms in a molecule), **constitutive** (these properties depend on the nature, number and arrangement of the atoms in the molecule), and **colligative** (these properties depend only on the number of molecules present, and are independent of their chemical constitution). It is extremely doubtful whether any one of these three classes of properties is absolutely independent of either or both of the others, except for the case of molecular weights, which may be regarded as truly additive and independent of the other two.

In constitutive and colligative properties, forces between molecules have a very great effect on these properties. Attractive forces between molecules of a substance must be assumed in order to explain cohesion in liquids and solids. Ideal gases obey the equation $PV = RT$, but real gases do not, partly because of the attractive forces between molecules. Van der Waals (1873) was the first to attempt to modify the ideal gas law for the behaviour of real gases by allowing for these attractive forces (he introduced the term a/v^2 to correct for them). These intermolecular forces are now usually referred to as *van der Waals forces*, but they are also known as *residual* or *secondary valencies*. These forces may be forces of attraction or forces of repulsion; the former explain cohesion, and the latter must be assumed to exist at short distances, otherwise molecules would collapse into one another when intermolecular distances become very small. The distances to which atoms held together by van der Waals forces can approach each other, *i.e.*, the distances at which the repulsion becomes very large, are known as *van der Waals radii*. Some values (in Angstroms) are:

H, 1·20; O, 1·40; N, 1·50; Cl, 1·80; S, 1·85.

These values are very useful in connection with molecules that exhibit the steric effect, *e.g.*, substituted diphenyl compounds (§2. V).

Van der Waals forces are electrostatic in nature. They are relatively weak forces (*i.e.*, in comparison with *bond* forces), but they are greater for compounds than for atoms and molecules of elements. In fact, the more asymmetrical the molecule, the greater are the van der Waals forces. These forces originate from three different causes:

(i) Forces due to the interaction between the permanent dipole moments of the molecules (Keesom, 1916, 1921). These forces are known as **Keesom forces** or the **dipole–dipole effect,** and are dependent on temperature.

(ii) Forces which result from the interaction of a *permanent* dipole and *induced* dipoles. Although a molecule may not possess a permanent dipole, nevertheless a dipole may be induced under the influence of neighbouring molecules which do possess a permanent dipole (Debye, 1920, 1921). These forces are known as **Debye forces,** the **dipole-induced dipole effect** or **induction effect,** and are almost independent of temperature.

(iii) London (1930) showed from wave mechanics that a third form of van der Waals forces is also acting. A nucleus and its " electron cloud " are in a state of vibration, and when two atoms are sufficiently close to each other, the two nuclei and the two electron clouds tend to vibrate together, thereby leading to attraction between different molecules. These forces are known as **London forces, dispersion forces,** or **the wave-mechanical effect,** and are independent of temperature.

It should be noted that the induced forces are smaller than the other two, and that the dispersion forces are usually the greatest.

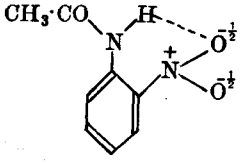
It can now be seen that all those physical properties which depend on intermolecular forces, *e.g.*, melting point, boiling point, viscosity, etc., will thus be largely determined by the van der Waals forces. Van der Waals forces may also be responsible for the formation of molecular complexes (see Vol. I).

§3. The hydrogen bond. A particularly important case of electrostatic attraction is that which occurs in *hydrogen bonding* (Vol. I, Ch. II); it occurs mainly in compounds containing hydroxyl or imino groups. There are two types of hydrogen bonding, *intermolecular* and *intramolecular*. Intermolecular bonding gives rise to association, thereby raising the boiling point; it also raises the surface tension and the viscosity, but lowers the dielectric constant. Intermolecular hydrogen bonding may exist in compounds in the liquid or solid state, and its formation is very much affected by the shape of

the molecules, *i.e.*, by the *spatial* or *steric* factor; *e.g.*, *n*-pentanol is completely associated, whereas *tert.*-pentanol is only partially associated. Intermolecular hydrogen bonding is also responsible for the formation of various molecular compounds, and also affects solubility if the compound can form hydrogen bonds with the solvent.

Intramolecular hydrogen bonding gives rise to *chelation*, *i.e.*, ring formation, and this normally occurs only with the formation of 5-, 6-, or 7-membered rings. Chelation has been used to explain the volatility of *ortho*-compounds such as *o*-halogenophenols and *o*-nitrophenols (as compared with the corresponding *m*- and *p*-derivatives). Chelation has also been used to account for various *ortho*-substituted benzoic acids being stronger acids than the corresponding *m*- and *p*-derivatives (see Vol. I, Ch. XXVIII).

When chelation occurs, the ring formed must be planar or almost planar. Should another group be present which prevents the formation of a *planar* chelate structure, then chelation will be diminished or even completely inhibited (Hunter *et al.*, 1938; *cf.* steric inhibition of resonance, Vol. I, Ch. XXVIII). Compound I is chelated, but II is associated and not chelated. In I the *o*-nitro-group can enter into the formation of a *planar* six-membered



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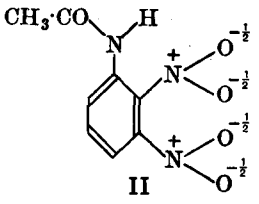

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ring. In II, owing to the strong repulsion between the negatively charged oxygen atoms of the two nitro-groups, the plane of each nitro-group will tend to be perpendicular to the plane of the benzene ring, and consequently a chelated *planar* six-membered ring cannot be formed.

The presence of hydrogen bonding may be detected by various means, *e.g.*, infra-red absorption spectra, X-ray analysis, electron diffraction, examination of boiling points, melting points, solubility, etc. The best method appears to be that of infra-red absorption spectra (see §15b).

§4. Melting point. In most solids the atoms or molecules are in a state of vibration about their fixed mean positions. These vibrations are due to the thermal energy and their amplitudes are small compared with interatomic distances. As the temperature of the solid is raised, the amplitude of vibration increases and a point is reached when the crystalline structure suddenly becomes unstable; this is the melting point.

In many homologous series the melting points of the *n*-members rise continuously, tending towards a maximum value. On the other hand, some homologous series show an alternation or oscillation of melting points—" the saw-tooth rule ", *e.g.*, in the fatty acid series the melting point of an " even " acid is higher than that of the " odd " acid immediately below and above it. It has been shown by X-ray analysis that this alternation of melting points depends on the packing of the crystals. The shape of the molecule is closely related to the melting point; the more symmetrical the molecule, the higher is the melting point. Thus with isomers, branching of the chain (which increases symmetry) usually raises the melting point; also *trans*-isomers usually have a higher melting point than the *cis*-, the former having greater symmetry than the latter (see §5. IV). In the benzene series, of the three disubstituted derivatives, the *p*-compound usually has the highest melting point.

Apart from the usual van der Waals forces which affect melting points

hydrogen bonding may also play a part, *e.g.*, the melting point of an alcohol is higher than that of its corresponding alkane. This may be attributed to hydrogen bonding, which is possible in the former but not in the latter.

Various *empirical* formulæ have been developed from which it is possible to calculate melting points; these formulæ, however, only relate members of an *homologous* series.

The method of mixed melting points has long been used to identify a compound, and is based on the principle that two different compounds mutually lower the melting point of each component in the mixture. This method, however, is unreliable when the two compounds form a solid solution.

§5. Boiling point. The boiling point of a liquid is that temperature at which the vapour pressure is equal to that of the external pressure. Thus the boiling point varies with the pressure, being raised as the pressure is increased.

In an homologous series, the boiling point usually increases regularly for the *n*-members, *e.g.*, Kopp (1842) found that with the aliphatic alcohols, acids, esters, etc., the boiling point is raised by 19° for each increase of CH_2 in the composition. In the case of isomers the greater the branching of the carbon chain, the lower is the boiling point. Calculation has shown that the boiling point of the *n*-alkanes should be proportional to the number of carbon atoms in the molecule. This relationship, however, is not observed in practice, and the cause of this deviation still remains to be elucidated. One strongly favoured theory attributes the cause to the fact that the carbon chains of *n*-alkanes in the liquid phase exist largely in a coiled configuration. As the branching increases, the coil becomes denser, and this lowers the boiling point.

In aromatic disubstituted compounds the boiling point of the *ortho*-isomer is greater than that of the *meta*-isomer which, in turn, may have a higher boiling point than the *para*-isomer, but in many cases the boiling points are about the same.

Since the boiling point depends on the van der Waals forces, any structural change which affects these forces will consequently change the boiling point. One such structural change is the branching of the carbon chain (see above). Another type of change is that of substituting hydrogen by a negative group. This introduces a dipole moment (or increases the value of an existing dipole moment), thereby increasing the attractive forces between the molecules and consequently raising the boiling point, *e.g.*, the boiling points of the nitro-alkanes are very much higher than those of the corresponding alkanes. The possibility of intermolecular hydrogen bonding also raises the boiling point, *e.g.*, alcohols boil at higher temperatures than the corresponding alkanes.

§6. Solubility. It is believed that solubility depends on the following intermolecular forces: solvent/solute; solute/solute; solvent/solvent. The solubility of a non-electrolyte in water depends, to a very large extent, on whether the compound can form hydrogen bonds with the water, *e.g.*, the alkanes are insoluble, or almost insoluble, in water. Methane, however, is more soluble than any of its homologues. The reason for this is uncertain; hydrogen bonding with water is unlikely, and so other factors must play a part, *e.g.*, molecular size. A useful guide in organic chemistry is that "like dissolves like", *e.g.*, if a compound contains a hydroxyl group, then the best solvents for that compound also usually contain hydroxyl groups (hydrogen bonding between solvent and solute is possible). This "rule" is accepted by many who use the word "like" to mean that the cohesion forces in both solvent and solute arise from the same source, *e.g.*, alkanes

and alkyl halides are miscible; the cohesion forces of both of these groups of compounds are largely due to dispersion forces.

In some cases solubility may be due, at least partly, to the formation of a compound between the solute and the solvent, *e.g.*, ether dissolves in concentrated sulphuric acid with the formation of an oxonium salt, $(C_2H_5)_2OH\}^+HSO_4^-$.

§7. Viscosity. Viscosity (the resistance to flow due to the internal friction in a liquid) depends, among other factors, on the van der Waals forces acting between the molecules. Since these forces depend on the shape and size of the molecules, the viscosity will also depend on these properties. At the same time, since the Keesom forces (§2) depend on temperature, viscosity will also depend on temperature; other factors, however, also play a part.

A number of relationships have been found between the viscosity of pure liquids and their chemical structure, *e.g.*,

(i) In an homologous series, viscosity increases with the molecular weight.

(ii) With isomers the viscosity of the *n*-compound is greater than that of isomers with branched carbon chains.

(iii) Abnormal viscosities are shown by *associated* liquids. Viscosity measurements have thus been used to determine the degree of association in liquids.

(iv) The viscosity of a *trans*-compound is greater than that of the corresponding *cis*-isomer.

Equations have been developed relating viscosity to the shape and size of *large* molecules (*macromolecules*) in solution, and so viscosity measurements have offered a means of determining the shape of, *e.g.*, proteins, and the molecular weight of, *e.g.*, polysaccharides.

§8. Molecular volumes. The molecular volume of a liquid in millilitres (V_m) is given by the equation

$$V_m = \frac{\text{gram molecular weight}}{\text{density}}$$

The relation between molecular volume and chemical composition was studied by Kopp (1839–1855). Since the density of a liquid varies with the temperature, it was necessary to choose a standard temperature for comparison. Kopp chose the boiling point of the liquid as the standard temperature. This choice was accidental, but proved to be a fortunate one since the absolute boiling point of a liquid at atmospheric pressure is approximately two-thirds of the critical temperature, *i.e.*, Kopp unknowingly compared liquids in their corresponding states, the theory of which did not appear until 1879. As a result of his work, Kopp was able to compile a table of atomic volumes based on the assumption that the molecular volume was an additive property, *e.g.*,

C	11·0	Cl	22·8
H	5·5	Br	27·8
O (C=O)	12·2	I	37·5
O(OH)	7·8		

It should be noted that Kopp found that the atomic volume of oxygen (and sulphur) depended on its state of combination. Kopp also showed that the molecular volume of a compound can be calculated from the sum of the atomic volumes, *e.g.*, acetone, $CH_3{\cdot}CO{\cdot}CH_3$.

3C	= 33·0	Molecular weight of acetone	= 58
6H	= 33·0	Density at b.p.	= 0·749
O(CO)	= 12·2	$\therefore$ molecular volume (*obs.*) $= \frac{58}{0{\cdot}749} = 77{\cdot}4$	
	78·2 (*calc.*)		

Further work has shown that the molecular volume is not strictly additive, but also partly constitutive (as recognised by Kopp who, however, tended to overlook this feature). If purely additive, then isomers with *similar* structures will have the same molecular volume. This has been found to be the case for, *e.g.*, isomeric esters, but when the isomers belong to different homologous series, the agreement may be poor.

Later tables have been compiled for atomic volumes with structural corrections. Even so, the relation breaks down in the case of highly polar liquids where the attractive forces between the molecules are so great that the additive (and structural) properties of the atomic volumes are completely masked.

§9. Parachor. Macleod (1923) introduced the following equation:

$$\gamma = C(d_l - d_g)^4$$

where γ is the surface tension, d_l and d_g the densities of the liquid and vapour respectively, and C is a constant which is independent of the temperature.

Macleod's equation can be rewritten as:

$$\frac{\gamma^{\frac{1}{4}}}{d_l - d_g} = C^{\frac{1}{4}}$$

Sugden (1924) multiplied both sides of this equation by the molecular weight, M, and pointed out that the expression

$$\frac{M\gamma^{\frac{1}{4}}}{d_l - d_g} = MC^{\frac{1}{4}} = [P]$$

should also be valid. Sugden called the constant P for a given compound the *parachor* of that compound. Provided the temperature is not too high, d_g will be negligible compared with d_l, and so we have

$$[P] = \frac{M\gamma^{\frac{1}{4}}}{d_l}$$

Hence the parachor represents the molecular volume of a liquid at the temperature when its surface tension is unity. Thus a comparison of parachors of different liquids gives a comparison of molecular volumes at temperatures at which liquids have the same surface tension. By this means allowance is made for the van der Waals forces, and consequently the comparison of molecular volumes is carried out under comparable conditions.

The parachor is largely an additive property, but it is also partly constitutive. The following table of atomic and structural parachors is that given by Mumford and Phillips (1929).

C	9·2	Single bond	0
H	15·4	Co-ordinate bond	0
O	20	Double bond	19
N	17·5	Triple bond	38
Cl	55	3-Membered ring	12·5
Br	69	4- ,, ,,	6
I	90	5- ,, ,,	3
S	50	6- ,, ,,	0·8
		7- ,, ,,	− 4

The parachor has been used to enable a choice to be made between alternative structures, *e.g.*, structures I and II had been suggested for *p*-benzoquinone. Most of the chemical evidence favoured I, but Graebe

(1867) proposed II to explain some of the properties of this compound (see Vol. I). The parachor has been used to decide between these two:

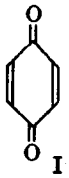
[P] calculated for I is 233·6;

$$[6 \times 9{\cdot}2 + 4 \times 15{\cdot}4 + 2 \times 20 + 4 \times 19 + 0{\cdot}8]$$

[P] calculated for II is 215·4;

$$[6 \times 9{\cdot}2 + 4 \times 15{\cdot}4 + 2 \times 20 + 3 \times 19 + 2 \times 0{\cdot}8]$$

[P] observed is 236·8. This indicates structure I.



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According to Sutton (1952), the parachor is not a satisfactory property for the analysis of molecular structure. It is, however, still useful as a physical characteristic of the liquid-vapour system.

§10. Refrachor. Joshi and Tuli (1951) have introduced a new physical constant which they have named the *refrachor*, [F]. This has been obtained by associating the parachor, [P], with the refractive index, (n_D^{20}), according to the following equation:

$$[F] = -[P] \log (n_D^{20} - 1)$$

The authors have found that the observed refrachor of any compound is composed of two constants, one dependent on the nature of the atoms, and the other on structural factors, *e.g.*, type of bond, size of ring, etc., *i.e.*, the refrachor is partly additive and partly constitutive. Joshi and Tuli have used the refrachor to determine the percentage of tautomers in equilibrium mixtures, *e.g.*, they found that ethyl acetoacetate contains 7·7 per cent. enol, and penta-2 : 4-dione 72·4 per cent. enol.

§11. Refractive index. Lorentz and Lorenz (1880) simultaneously showed that

$$R = \frac{n^2 - 1}{n^2 - 2} \cdot \frac{M}{d}$$

where R is the *molecular refractivity*, n the refractive index, M the molecular weight, and d the density. The value of n depends on the wavelength and on temperature; d depends on temperature.

Molecular refractivity has been shown to have both additive and constitutive properties. The following table of atomic and structural refractivities has been calculated for the H_α line.

C	2·413	Cl	5·933
H	1·092	Br	8·803
O(OH)	1·522	I	13·757
O(CO)	2·189	Double bond (C=C)	1·686
O(ethers)	1·639	Triple bond (C≡C)	2·328

Molecular refractivities have been used to determine the structure of compounds, *e.g.*, terpenes (see §25. VIII). They have also been used to detect the presence of tautomers and to calculate the amount of each form present. Let us consider ethyl acetoacetate as an example; this behaves as the keto form $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5$, and as the enol form $CH_3{\cdot}C(OH){=}CH{\cdot}CO_2C_2H_5$.

The calculated molecular refractivities of these forms are:

$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2C_2H_5$		$CH_3{\cdot}C(OH){=}CH{\cdot}CO_2C_2H_5$	
6 C	= 14·478	6 C	= 14·478
10 H	= 10·92	10 H	= 10·92
2 O (CO)	= 4·378	O (OH)	= 1·522
O (ether)	= 1·639	O (CO)	= 2·189
	31·415	O (ether)	= 1·639
		Double bond	= 1·686
			32·434

The observed molecular refractivity of ethyl acetoacetate is 31·89; hence both forms are present.

When a compound contains two or more double bonds, the value of the molecular refractivity depends not only on their number but also on their relative positions. When the double bonds are *conjugated*, then anomalous results are obtained, the observed molecular refractivity being higher than that calculated, *e.g.*, the observed value for hexa-1 : 3 : 5-triene is 2·06 units greater than the value calculated. This anomaly is known as *optical exaltation*, and it usually increases with increase in length of conjugation (in unsubstituted chains). Although optical exaltation is characteristic of acyclic compounds, it is also exhibited by cyclic compounds. In single-ring systems, *e.g.*, benzene, pyridine, pyrrole, etc., the optical exaltation is negligible; this has been attributed to resonance. In polycyclic aromatic compounds, however, the exaltation may have a large value. In general, large exaltations are shown by those compounds which exhibit large *electronic* effects.

Another application of the refractive index is its relation to hydrogen bonding. Arshid *et al.* (1955, 1956) have used the square of the refractive index to detect hydrogen-bond complexes.

§12. Molecular rotation. When a substance possesses the property of rotating the plane of polarisation of a beam of plane-polarised light passing through it, that substance is said to be **optically active.** The measurement of the **rotatory power** of a substance is carried out by means of a polarimeter. If the substance rotates the plane of polarisation to the right, *i.e.*, the analyser has to be turned to the right (clockwise) to restore the original field, the substance is said to be *dextrorotatory*; if to the left (anti-clockwise), *lævorotatory*.

It has been found that the amount of the rotation depends, for a given substance, on a number of factors:

(i) *The thickness of the layer traversed.* The amount of the rotation is directly proportional to the length of the active substance traversed (Biot, 1835).

(ii) *The wavelength of the light.* The rotatory power is approximately inversely proportional to the square of the wavelength (Biot, 1835). There are some exceptions, and in certain cases it has been found that the rotation changes sign. This change in rotatory power with change in wavelength is known as *rotatory dispersion.* Hence it is necessary (for comparison of rotatory power) to use monochromatic light; the sodium D line (yellow: 5893 A) is one wavelength that is commonly used (see also §12a).

(iii) *The temperature.* The rotatory power usually increases with rise in temperature, but many cases are known where the rotatory power decreases. Hence, for comparison, it is necessary to state the temperature; in practice, measurements are usually carried out at 20 or 25°.

(iv) *The solvent.* The nature of the solvent affects the rotation, and so it is necessary to state the solvent used in the measurement of the rotatory

power. There appears to be some relation between the effect of a solvent on rotatory power and its dipole moment.

(v) *The concentration.* The rotation appears to be independent of the concentration provided that the solution is dilute. In concentrated solutions, however, the rotation varies with the concentration; the causes for this have been attributed to association, dissociation, or solvation (see also vi).

(vi) The amount of rotation exhibited by a given substance when all the preceding factors (i–v) have been fixed may be varied by the presence of other compounds which are not, in themselves, optically active, *e.g.*, inorganic salts. It is important to note in this connection that optically active acids or bases, in the form of their salts, give rotations which are independent of the nature of the non-optically active ion *provided that the solutions are very dilute.* In very dilute solutions, salts are completely dissociated, and it is only the optically active ion which then contributes to the rotation. The rotation of a salt formed from an optically active acid and an optically active base reaches a constant value in dilute solutions, and the rotation is the sum of the rotations of the anion and cation. This property has been used to detect optical activity (see §5a. VI).

When recording the rotations of substances, the value commonly given is the **specific rotation,** $\left[\alpha\right]_{\lambda}^{t}$. This is obtained from the equation:

$$\left[\alpha\right]_{\lambda}^{t} = \frac{\alpha_{\lambda}^{t}}{l \times d} \quad or \quad \left[\alpha\right]_{\lambda}^{t} = \frac{\alpha_{\lambda}}{l \times c}$$

where l is the thickness of the layer in decimetres, d the density of the liquid (if it is a pure compound), c the number of grams of substance per millilitre of solution (if a solution is being examined), α the *observed* rotation, t the temperature and λ the wavelength of the light used. The solvent should also be stated (see iv).

The **molecular rotation,** $\left[\mathrm{M}\right]_{\lambda}^{t}$, is obtained by multiplying the specific rotation by the molecular weight, M. Since large numbers are usually obtained, a common practice is to divide the result by one hundred; thus:

$$\left[\mathrm{M}\right]_{\lambda}^{t} = \frac{\left[\alpha\right]_{\lambda}^{t} \times \mathrm{M}}{100}$$

The relation between structure and optical activity is discussed later (see §§2, 3. II). The property of optical activity has been used in the study of the configuration of molecules and mechanisms of various reactions, and also to decide between alternative structures for a given compound. The use of optical rotations in the determination of structure depends largely on the application of two rules.

(i) **Rule of Optical Superposition** (van't Hoff, 1894): When a compound contains two or more asymmetric centres, the total rotatory power of the molecules is the algebraic sum of the contributions of each asymmetric centre. This rule is based on the assumption that the contribution of each asymmetric centre is independent of the other asymmetric centres present. It has been found, however, that the contribution of a given asymmetric centre is affected by neighbouring centres and also by the presence of chain-branching and unsaturation. Hence the rule, although useful, must be treated with reserve (see also §6. VII).

A more satisfactory rule is the **Rule of Shift** (Freudenberg, 1933): If two asymmetric molecules A and B are changed in the same way to give A′ and B′, then the differences in molecular rotation (A′ — A) and (B′ — B) are of the same sign (see, *e.g.*, §4b. XI).

(ii) **Distance Rule** (Tschugaev, 1898): The effect of a given structural change on the contribution of an asymmetric centre decreases the further the centre of change is from the asymmetric centre.

Only asymmetric molecules have the power, under normal conditions, to rotate the plane of polarisation (of plane-polarised light). Faraday (1845), however, found that any transparent substance can rotate the plane of polarisation when placed in a strong magnetic field. This property of **magnetic optical rotation (Faraday effect)** is mainly an additive one, but is also partly constitutive.

§12a. Rotatory dispersion. In §12 we have discussed the method of optical rotations using *monochromatic rotations*. There is also, however, the method of *rotatory dispersion*. Optical rotatory dispersion is the change in rotatory power with change in wavelength, and rotatory dispersion measurements are valuable only for asymmetric compounds. In order to study the essential parts of dispersion curves, it is necessary to measure the optical rotation of a substance right through an absorption band of that substance. This is experimentally possible only if this absorption band is in an accessible part of the spectrum. Up to the present, the carbonyl group ($\lambda_{max.}$ at 280–300 mμ) is the only convenient absorbing group that fulfils the necessary requirements. Thus, at the moment, measurements are taken in the range 700 to 270 mμ.

There are three types of rotatory dispersion curves: (*a*) Plain curves; (*b*) single Cotton Effect curves; (*c*) multiple Cotton Effect curves. We shall describe (*a*) and (*b*); (*c*) shows two or more peaks and a corresponding number of troughs.

Plain curves. These show no maximum or minimum, *i.e.*, they are *smooth curves*, and may be positive or negative according as the rotation becomes more positive or negative as the wavelength changes from longer to shorter values (Fig. 1*a*).

Single Cotton Effect curves. These are also known as *anomalous curves* and show a maximum and a minimum, both of these occurring in the region

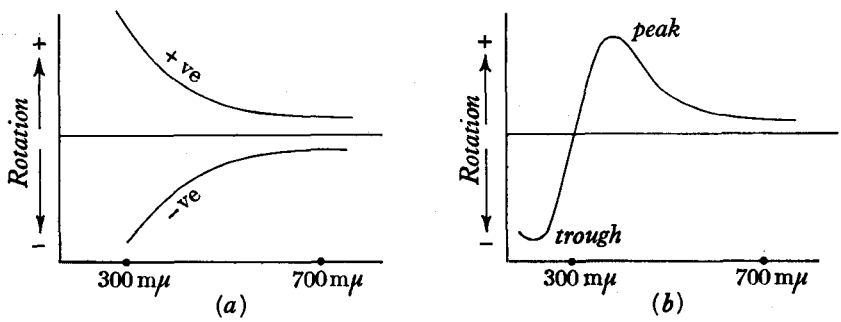

FIG. 1.1.

of maximum absorption (Fig. 1 *b*). The curves are said to be positive or negative according as the peak or trough occurs in the longer wavelength. Thus the curve shown in Fig. 1 (*b*) is positive.

As pointed out above, to obtain single Cotton Effect curves (see also §8. III) the molecule must contain a carbonyl group. The wavelength of maximum ultraviolet absorption is referred to as " the optically active absorption band ", and since rotatory dispersion measurements are of value only for asymmetric compounds, to obtain suitable curves compounds containing a carbonyl group in an asymmetric environment must be used. Enantiomorphs have curves which are mirror images of each other; compounds

which are enantiomorphic in the neighbourhood of the carbonyl group have dispersion curves which are approximately mirror images of each other; and compounds which have the same relative configurations in the neighbourhood of the carbonyl group have dispersion curves of the same sign.

There are many applications of rotatory dispersion: (i) quantitative analytical uses; (ii) identification of the carbonyl group; (iii) location of carbonyl groups; (iv) the determination of relative configurations; (v) the determination of absolute configurations; (vi) the determination of conformation. Some examples of these applications are described in the text (see Index).

§13. Dipole moments. When the centres of gravity of the electrons and nuclei in a molecule do not coincide, the molecule will possess a *permanent* dipole moment, μ, the value of which is given by $\mu = e \times d$, where e is the electronic charge, and d the distance between the charges (positive and negative centres). Since e is of the order of 10^{-10} e.s.u., and d 10^{-8} cm., μ is therefore of the order 10^{-18} e.s.u. This unit is known as the Debye (D), in honour of Debye, who did a great deal of work on dipole moments.

The dipole moment is a vector quantity, and its direction in a molecule is often indicated by an arrow parallel to the line joining the points of charge, and pointing towards the negative end, *e.g.*, $\overset{+}{\text{H}}\!\!\rightarrow\!\!\overset{-}{\text{Cl}}$ (Sidgwick, 1930). The greater the value of the dipole moment, the greater is the *polarity* of the bond. It should be noted that the terms *polar* and *non-polar* are used to describe bonds, molecules and groups. Bond dipoles are produced because of the different electron-attracting powers of atoms (or groups) joined by that bond. This unequal electronegativity producing a dipole moment seems to be a satisfactory explanation for many simple molecules, but is unsatisfactory in other cases. Thus a number of factors must operate in determining the value of the dipole moment. It is now believed that *four* factors contribute to the bond moment:

(i) The unequal sharing of the bonding electrons arising from the different electronegativities of the two atoms produces a dipole moment.

(ii) In covalent bonds a dipole is produced because of the difference in size of the two atoms. The centres of gravity (of the charges) are at the nucleus of each contributing atom. Thus, if the atoms are different in size, the resultant centre of gravity is not at the mid-point of the bond, and so a bond moment results.

(iii) Hybridisation of orbitals produces asymmetric atomic orbitals; consequently the centres of gravity of the hybridised orbitals are no longer at the parent nuclei. Only if the orbitals are pure s, p or d, are the centres of gravity at the parent nuclei. Thus hybridised orbitals produce a bond moment.

(iv) Lone-pair electrons (*e.g.*, on the oxygen atom in water) are not "pure" s electrons; they are "impure" because of hybridisation with p electrons. If lone-pair electrons were not hybridised, their centre of gravity would be at the nucleus; hybridisation, however, displaces the centre of gravity from the nucleus and so the asymmetric orbital produced gives rise to a bond moment which may be so large as to outweigh the contributions of the other factors to the dipole moment.

The following points are useful in organic chemistry:

(i) In the bond H—Z, where Z is any atom other than hydrogen or carbon, the hydrogen atom is the positive end of the dipole, *i.e.*, $\overset{+}{\text{H}}\!\!\rightarrow\!\!\text{Z}$.

(ii) In the bond C—Z, where Z is any atom other than carbon, the carbon atom is the positive end of the dipole, *i.e.*, $\text{C}\!\!\rightarrow\!\!\overset{-}{\text{Z}}$ (Coulson, 1942).

(iii) When a molecule contains two or more polar bonds, the resultant dipole moment of the molecule is obtained by the vectorial addition of the constituent bond dipole moments. A symmetrical molecule will thus be non-polar, although it may contain polar bonds, *e.g.*, CCl_4 has a zero dipole moment although each C—Cl bond is strongly polar.

Since dipole moments are vector quantities, the sum of two equal and opposite group moments will be zero only if the two vectors are collinear or parallel. When the group moment is directed along the axis of the bond formed by the " key " atom of the group and the carbon atom to which it is joined, then that group is said to have a *linear* moment. Such groups are H, halogen, Me, CN, NO_2, etc. On the other hand, groups which have *non-linear* moments are OH, OR, CO_2H, NH_2, etc. This problem of linear or non-linear group moments has a very important bearing on the use of dipole data in, *e.g.*, elucidating configurations of geometrical isomers (see §5. IV), orientation in benzene derivatives (see Vol. I).

When any molecule (polar or non-polar) is placed in an electric field, the electrons are displaced from their normal positions (towards the positive pole of the external field). The positive nuclei are also displaced (towards the negative pole of the external field), but their displacement is much less than that of the electrons because of their relatively large masses. These displacements give rise to an *induced* dipole, and this exists only while the external electric field is present. The value of the induced dipole depends on the strength of the external field and on the *polarisability* of the molecule, *i.e.*, the ease with which the charged centres are displaced by the external field. If P is the total dipole moment, P_μ the permanent dipole moment, and P_α the induced dipole moment, then

$$P = P_\mu + P_\alpha$$

P_μ decreases as the temperature rises, but P_α is independent of the temperature. The value of P *in solution* depends on the nature of the solvent and on the concentration.

By means of dipole moment measurements, it has been possible to get a great deal of information about molecules, *e.g.*,

(i) Configurations of molecules have been ascertained, *e.g.*, water has a dipole moment and hence the molecule cannot be linear. In a similar way it has been shown that ammonia and phosphorus trichloride are not flat molecules.

(ii) Orientations in benzene derivatives have been examined by dipole moments (see Vol. I). At the same time, this method has shown that the benzene molecule is flat.

(iii) Dipole moment measurements have been used to distinguish between geometrical isomers (see §5. IV).

(iv) Dipole moments have been used to demonstrate the existence of resonance and to elucidate electronic structures.

(v) Energy differences between different conformations (see §4a. II) have been calculated from dipole moment data.

(vi) The existence of dipole moments gives rise to association, the formation of molecular complexes, etc.

§14. Magnetic susceptibility. When a substance is placed in a magnetic field, the substance may or may not become magnetised. If I is the *intensity of magnetisation* induced, and H the strength of the magnetic field inducing it, then the **magnetic susceptibility,** κ, is given by

$$\kappa = \frac{I}{H}$$

The *magnetic induction*, B, is given by

$$B = H + 4\pi I$$

$$\text{Since } I = \kappa H, \quad B = H(1 + 4\pi\kappa)$$

The quantity $1 + 4\pi\kappa$ is called the *magnetic permeability*, μ.

Elements other than iron, nickel and cobalt (which are *ferromagnetic*) may be divided into two groups:

(i) **Paramagnetic:** in this group μ is greater than unity and κ is therefore positive.

(ii) **Diamagnetic:** in this group μ is less than unity and κ is therefore negative.

All compounds are either paramagnetic or diamagnetic. Paramagnetic substances possess a permanent magnetic moment and consequently orient themselves along the external magnetic field. Diamagnetic substances do not possess a permanent magnetic moment, and tend to orient themselves at right angles to the external magnetic field.

Electrons, because of their spin, possess magnetic dipoles. When electrons are paired (*i.e.*, their spins are anti-parallel), then the magnetic field is cancelled out. Most organic compounds are diamagnetic, since their electrons are paired. " Odd electron molecules ", however, are paramagnetic (see also §19).

Magnetic susceptibility has been used to obtain information on the nature of bonds and the configuration of co-ordination compounds. Organic compounds which are paramagnetic are generally free radicals (odd electron molecules), and the degree of dissociation of, *e.g.*, hexaphenylethane into triphenylmethyl has been measured by means of its magnetic susceptibility.

§15. Absorption spectra. When light (this term will be used for electromagnetic waves of any wavelength) is absorbed by a molecule, the molecule undergoes transition from a state of lower to a state of higher energy. If the molecule is monatomic, the energy absorbed can only be used to raise the energy levels of electrons. If, however, the molecule consists of more than one atom, the light absorbed may bring about changes in electronic, rotational or vibrational energy. Electronic transitions give absorption (or emission) in the visible and ultraviolet parts of the spectrum, whereas rotational and vibrational changes give absorption (or emission) respectively in the far and near infra-red. Electronic transitions may be accompanied by the other two. A study of these energy changes gives information on the structure of molecules.

Spectrum	*Wavelength (A)*
Ultraviolet	2000–4000
Visible	4000–7500
Near infra-red	$7500–15 \times 10^4$
Far infra-red	$15 \times 10^4–100 \times 10^4$

The position of the absorption band can be given as the wavelength λ (cm., μ, A, mμ) or as the wave number, $\tilde{\nu}$ (cm.$^{-1}$).

1 μ (micron) $= 10^{-3}$ mm. 1 mμ (millimicron) $= 10^{-6}$ mm.
1 A (Angstrom) $= 10^{-8}$ cm. $= 10^{-7}$ mm. 1 mμ $= 10$ A.

$$\lambda\ (\mu) = \frac{10^4}{\tilde{\nu}\ (\text{cm.}^{-1})}$$

$$\tilde{\nu}\ (\text{cm.}^{-1}) = \frac{1}{\lambda\ (\text{cm.})} = \frac{10^4}{\lambda\ (\mu)} = \frac{10^8}{\lambda\ (\text{A})}$$

If I_0 is the intensity of an incident beam of monochromatic light, and I that of the emergent beam which has passed through an absorbing medium of thickness l, then

$$I = I_0 10^{-\varepsilon l} \qquad or \qquad \log_{10} \frac{I_0}{I} = \varepsilon l$$

where ε is the *extinction coefficient* of the medium. The ratio I_0/I is called the *transmittance* of the medium, and the reciprocal the *opacity*; the function $\log_{10} I_0/I$ is called the *density* (d).

If the absorbing substance is in solution (the solvent being *colourless*), and if c is the concentration (number of grams per litre), then

$$I = I_0 10^{-\varepsilon cl}$$

This equation is **Beer's law** (1852), and is obeyed by most solutions provided they are *dilute*. In more concentrated solutions there may be divergencies from Beer's law, and these may be caused by association, changes in solvation, etc.

If the extinction coefficient is plotted against the wavelength of the light used, the *absorption curve* of the compound is obtained, and this is characteristic for a *pure* compound (under identical conditions).

§15a. Ultraviolet and visible absorption spectra. When a molecule absorbs light, it will be raised from the ground state to an excited state. The position of the absorption band depends on the difference between the energy levels of the ground and excited states. Any change in the structure of the molecule which alters the energy difference between the ground and excited states will thus affect the position of the absorption band. This shifting of bands (in the ultraviolet and visible regions) is concerned with the problem of colour (see Vol. I, Ch. XXXI).

With few exceptions, only molecules containing multiple bonds give rise to absorption in the near ultraviolet. In compounds containing only one multiple-bond group, the intensity of the absorption maxima may be very low, but when several of these groups are present in conjugation, the absorption is strong, *e.g.*, an isolated oxo (carbonyl) group has an absorption at $\lambda_{max.}$ 2750 A; an isolated ethylene bond has an absorption at $\lambda_{max.}$ 1950 A. When a compound contains an oxo group conjugated with an ethylenic bond, *i.e.*, the compound is an $\alpha\beta$-unsaturated oxo compound, the two bands no longer occur in their original positions, but are shifted to 3100–3300 A and 2200–2600 A, respectively. Thus, in a compound in which the presence of an ethylenic bond and an oxo group has been demonstrated (by chemical methods), it is also possible to tell, by examination of the ultraviolet absorption spectrum, whether the two groups are conjugated or not (see, *e.g.*, cholestenone, §3 (ii). XI).

Ultraviolet and visible absorption spectra have also been used to differentiate between geometrical isomers and to detect the presence or absence of restricted rotation in diphenyl compounds (§2. V).

§15b. Infra-red spectra. In a molecule which has some definite configuration, the constituent atoms vibrate with frequencies which depend on the masses of the atoms and on the restoring forces brought into play when the molecule is distorted from its equilibrium configuration. The energy for these vibrations is absorbed from the incident light, and thereby gives rise to a vibrational spectrum. A given bond has a characteristic absorption band, but the frequency depends, to some extent, on the nature of the other atoms joined to the two atoms under consideration. It is thus possible to ascertain the nature of bonds (and therefore groups) in unknown compounds by comparing their infra-red spectra with tables of infra-red absorption spectra. At the same time it is also possible to verify tentative structures (obtained from chemical evidence) by comparison with spectra of *similar* compounds of known structure.

The study of infra-red spectra leads to information on many types of problems, *e.g.*,

(i) Infra-red spectroscopy has been used to distinguish between geo-

metrical isomers, and recently Kuhn (1950) has shown that the spectra of the stereoisomers methyl α- and β-glycosides are different. It also appears that enantiomorphs in the *solid* phase often exhibit different absorption spectra. Infra-red spectroscopy has also been a very valuable method in conformational studies (see §11. IV).

(ii) The three isomeric disubstituted benzenes have characteristic absorption bands, and this offers a means of determining their orientation.

(iii) Infra-red spectroscopy has given a great deal of information about the problem of free rotation about a single bond; *e.g.*, since the intensity of absorption is proportional to the concentration, it has been possible to ascertain the presence and amounts of different conformations in a mixture (the intensities vary with the temperature when two or more conformations are present).

(iv) Tautomeric mixtures have been examined and the amounts of the tautomers obtained. In many cases the *existence* of tautomerism can be ascertained by infra-red spectroscopy (*cf.* iii).

(v) Infra-red spectroscopy appears to be the best means of ascertaining the presence of hydrogen bonding (both in association and chelation). In " ordinary " experiments it is not possible to distinguish between intra- and intermolecular hydrogen bonding. These two modes of bonding can, however, be differentiated by obtaining a series of spectra at different dilutions. As the dilution increases, the absorption due to intermolecular hydrogen bonding decreases, whereas the intramolecular hydrogen-bonding absorption is unaffected.

(vi) It is possible to evaluate dipole moments from infra-red spectra.

(vii) When a bond between two atoms is stretched, a restoring force immediately operates. If the distortion is *small*, the restoring force may be assumed to be directly proportional to the distortion, *i.e.*,

$$f \propto d \quad or \quad f = kd$$

where k is the *stretching force constant* of the bond. It is possible to calculate the values of these force constants from infra-red (vibrational) spectra.

(viii) The far infra-red or micro-wave region contains the *pure rotational* spectrum. Micro-wave spectroscopy (a recent development) offers a very good method for measuring bond lengths. It is possible to calculate atomic radii from bond lengths, but the value depends on whether the bond is single, double or triple, and also on the charges (if any) on the atoms concerned. Thus the character of a bond can be ascertained from its length, *e.g.*, if a bond length (determined experimentally) differs significantly from the sum of the atomic radii, then the bond is not " normal ". Resonance may be the cause of this.

Some atomic covalent radii (in Angstroms) are:

H	0·30	N (single)	0·70	Cl	0·99
C (single)	0·77	N (double)	0·61	Br	1·14
C (double)	0·67	N (triple)	0·55	I	1·33
C (triple)	0·60	O (single)	0·66	S	1·04
		O (double)	0·57		

Micro-wave spectroscopy is particularly useful for information on the molecular structure of polar gases, and is also used for showing the presence of free radicals.

§15c. Raman spectra. When a beam of monochromatic light passes through a transparent medium, most of the light is transmitted or scattered without change in wavelength. Some of the light, however, is converted into *longer* wavelengths, *i.e.*, *lower* frequency (a smaller amount of the light may be changed into shorter wavelengths, *i.e.*, higher frequency). The

change from *higher to lower* frequency is known as the **Raman effect (Raman shift).** It is independent of the frequency of the light used, but is characteristic for a given bond.

Raman spectra have been used to obtain information on structure, *e.g.*, the Raman spectrum of formaldehyde in aqueous solution shows the absence of the oxo group, and so it is inferred that formaldehyde is hydrated: $CH_2(OH)_2$. Raman spectra have also been used to ascertain the existence of keto-enol tautomerism and different conformations, to provide evidence for resonance, to differentiate between geometrical isomers, to show the presence of association, and to give information on force constants of bonds.

§16. X-ray analysis. X-rays may be used with gases, liquids or solids, but in organic chemistry they are usually confined to solids, which may be single crystals, or substances consisting of a mass of minute crystals (*powder method*), or fibres. When X-rays (wavelength 0·7–1·5 A) fall on solids, they are diffracted to produce patterns (formed on a photographic film). Since X-rays are diffracted mainly by the orbital electrons of the atoms, the diffraction will be a function of the atomic number. Because of this, it is difficult to differentiate between atoms whose atomic numbers are very close together, *e.g.*, carbon and nitrogen. Furthermore, since the scattering power of hydrogen atoms (for X-rays) is very low, it is normally impossible to locate these atoms except in very favourable conditions, and then only with fairly simple compounds.

Two problems are involved in the interpretation of X-ray diffraction patterns, *viz.*, the dimensions of the unit cell and the positions of the individual atoms in the molecule. The positions of the diffracted beams depend on the dimensions of the unit cell. A knowledge of these dimensions leads to the following applications:

(i) Identification of substances; this is done by looking up tables of unit cells.

(ii) Determination of molecular weights. If V is the volume of the unit cell, d the density of the compound, and n the number of molecules in a unit cell, then the molecular weight, M, is given by

$$M = \frac{Vd}{n}$$

(iii) Determination of the shapes of molecules. Many long-chain polymers exist as fibres, *e.g.*, cellulose, keratin. These fibres are composed of bundles of tiny crystals with one axis parallel, or nearly parallel, to the fibre axis. When X-rays fall on the fibre in a direction perpendicular to its length, then the pattern obtained is similar to that from a single crystal rotated about a principal axis. It is thus possible to obtain the unit cell dimensions of such fibres (see, *e.g.*, rubber, §33. VIII).

The intensities of the diffracted beams depend on the positions of the atoms in the unit cell. A knowledge of these relative intensities leads to the following applications:

(i) Determination of bond lengths, valency angles, and the general electron distribution in molecules.

(ii) Determination of molecular symmetry. This offers a means of distinguishing between geometrical isomers, and also of ascertaining the shape of a molecule, *e.g.*, the diphenyl molecule has a centre of symmetry, and therefore the two benzene rings must be coplanar (see §2. V).

(iii) Determination of structure. This application was originally used for compounds of *known* structure. Trial models based on the structure of the molecule were compared with the X-ray patterns, and if they "fitted", *confirmed* the structure already accepted. If the patterns did not fit, then it was necessary to look for another structural formula. More recently,

however, X-ray analysis has been applied to compounds of unknown or partially known structures, *e.g.*, penicillin (§6a. XVIII).

(iv) X-ray analysis has been used to elucidate the conformations of rotational isomers (§4a. II), and also to determine the *absolute* configurations of enantiomorphs (§5. II).

§17. Electron diffraction. Electron diffraction is another direct method for determining the spatial arrangement of atoms in a molecule, and is usually confined to gases or compounds in the vapour state, but may be used for solids and liquids. Electrons exhibit a dual behaviour, particle or wave, according to the nature of the experiment. The wavelength of electrons is inversely proportional to their momentum: the wavelength is about 0·06 A for the voltages generally used. Because of their small diffracting power, hydrogen atoms are difficult, if not impossible, to locate.

By means of electron diffraction it is possible to obtain values of bond lengths and the size and shape of molecules, particularly macromolecules. Electron diffraction studies have been particularly useful in the investigation of conformations in *cyclo*hexane compounds (see §11. IV).

§18. Neutron crystallography. A beam of *slow* neutrons is diffracted by crystalline substances. The equivalent wavelength of a slow beam of neutrons is 1 A, and since this is of the order of interatomic distances in crystals, the neutrons will be diffracted. This method of analysis is particularly useful for determining the positions of *light* atoms, a problem which is very difficult, and often impossible, with X-ray analysis. Thus neutron diffraction is extremely useful for locating hydrogen atoms.

In addition to studying solids, neutron diffraction has also been applied to gases, pure liquids and solutions.

§19. Electron spin resonance. Electrons possess spin (and consequently a magnetic moment) and are therefore capable of interacting with an external magnetic field. The spin of *one* electron of a *covalent* pair and its resulting interaction with a magnetic field is cancelled by the equal and opposite spin of its partner (see also §14). An *unpaired* electron, however, will have an interaction that is not cancelled out and the energy of its interaction may change if its spin changes to the opposite direction (an electron has a spin quantum number s; this can have values of $+\frac{1}{2}$ and $-\frac{1}{2}$). For an unpaired electron to change the sign of its spin in a magnetic field in the direction of greater energy, it must *absorb* energy, and it will do this if electromagnetic energy of the *appropriate* wavelength is supplied. By choosing a suitable strength for the magnetic field, the unpaired electron can be made to absorb in the micro-wave region; a field of about 3000 gauss is usually used in conjunction with radiation of a frequency in the region of 9 kMc./sec. This method of producing a spectrum is known as *electron spin resonance* (ESR) or *electron paramagnetic resonance* (EPR). ESR is used as a method for the study of free radicals; it affords a means of detecting and measuring the concentration of free radicals, and also supplies specific information about their structure. The application of ESR has shown that free radicals take part in photosynthesis.

§19a. Nuclear magnetic resonance. Just as electrons have spin, so have the protons and neutrons in atomic nuclei. In most nuclei the spins are not cancelled out and hence such nuclei possess a resultant nuclear magnetic moment. When the nucleus possesses a magnetic moment, the ground state consists of two or more energy levels which are indistinguishable from each other. Transition from one level to another, however, can be induced by absorption or emission of a quantum of radiation of the proper frequency which is determined by the energy difference between the

two nuclear levels. This frequency occurs in the radiofrequency region, and can be varied by changing the strength of the applied field. In this way is obtained the spectrum by the method of *nuclear magnetic resonance* (NMR). The resonance frequencies of most magnetic nuclei lie between 0·1 and 40 Mc. for fields varying from 1000 to 10,000 gauss.

Of particular importance are the nuclear properties of the proton; here we have the special case of NMR, *proton magnetic resonance.* A large proportion of the work in this field has been done with protons; protons give the strongest signals. Analysis of structure by NMR depends mainly on the fact that although the *same nucleus* is being examined, the NMR spectrum depends on the environment of that nucleus. This difference in resonance frequency has been called *chemical shift*; chemical shifts are small. Thus it is possible to identify C—H in saturated hydrocarbons and in olefins; a methyl group attached to a saturated carbon atom can be differentiated from one attached to an unsaturated one; etc.

NMR has been used to provide information on molecular structure, to identify molecules, and to examine the crystal structure of solids. It has also been used to measure keto-enol equilibria and for the detection of association, etc. NMR is also useful in conformational analysis (§4a. II) and for distinguishing between various *cis*- and *trans*-isomers (§5. IV).

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CHAPTER II

OPTICAL ISOMERISM

§1. **Stereoisomerism. Stereochemistry** is the " chemistry of space ", *i.e.*, stereochemistry deals with the *spatial* arrangements of atoms and groups in a molecule. **Stereoisomerism** is exhibited by isomers having the *same* structure but differing in their spatial arrangement, *i.e.*, having different *configurations*. Different configurations are possible because carbon forms mainly covalent bonds and these have direction in space. The covalent bond is formed by the overlapping of atomic orbitals, the bond energy being greater the greater the overlap of the component orbitals. To get the maximum overlap of orbitals, the orbitals should be in the same plane. Thus *non-spherical* orbitals tend to form bonds in the direction of the greatest concentration of the orbital, and this consequently produces a *directional* bond (see also Vol. I, Ch. II).

There are two types of stereoisomerism, **optical isomerism** and **geometrical isomerism** (***cis-trans* isomerism**). It is not easy to define them, but their meanings will become clear as the study of stereochemistry progresses. Even so, it is highly desirable to have some idea about their meanings at this stage, and so the following summaries are given.

Optical isomerism is characterised by compounds having the same structure but different configurations, and because of their *molecular asymmetry* these compounds rotate the plane of polarisation of plane-polarised light. Optical isomers have similar physical and chemical properties; the most marked difference between them is their action on plane-polarised light (see §12. I). Optical isomers may rotate the plane of polarisation by *equal* and *opposite* amounts; these optical isomers are **enantiomorphs** (see §4). On the other hand, some optical isomers may rotate the plane of polarisation by *different* amounts; these are **diastereoisomers** (see §7b). Finally, some optical isomers may possess no rotation at all; these are diastereoisomers of the ***meso*-**type (see §7d).

Geometrical isomerism is characterised by compounds having the same structure but different configurations, and because of their *molecular symmetry* these compounds do *not* rotate the plane of polarisation of plane-polarised light. Geometrical isomers differ in all their physical and in many of their chemical properties. They can also exhibit optical isomerism if the structure of the molecule, apart from giving rise to geometrical isomerism, is also asymmetric. In general, geometrical isomerism involves molecules which can assume different stable configurations, the ability to do so being due, *e.g.*, to the presence of a double bond, a ring structure, or the steric effect (see Ch. IV and V).

§2. **Optical isomerism.** It has been found that only those structures, crystalline or molecular, which are *not* superimposable on their mirror images, are optically active. Such structures may be *dissymmetric*, or *asymmetric*. Asymmetric structures have no elements of symmetry at all, but dissymmetric structures, although possessing some elements of symmetry, are nevertheless still capable of existing in two forms (one the mirror image of the other) which are not superimposable. To avoid unnecessary complications, we shall use the term asymmetric to cover both cases (of asymmetry and dissymmetry).

A given molecule which has at least one element of symmetry (§6) when its " classical " configuration (*i.e.*, the Fischer projection formula; §5) is

inspected may, however, have a conformation (§4a) which is devoid of any element of symmetry. At first sight, such a molecule might be supposed to be optically active. In practice, however, it is not; individual molecules are optically active, but statistically, the whole collection of molecules is not. It therefore follows that when a molecule can exist in one or more conformations, then provided that at least one of the conformations (whether preferred or not) is superimposable on its mirror image, the compound will not be optically active (see §11 for a discussion of this problem).

Optical activity due to crystalline structure. There are many substances which are optically active in the solid state only, *e.g.*, quartz, sodium chlorate, benzil, etc. Let us consider quartz, the first substance shown to be optically active (Arago, 1811). Quartz exists in two crystalline forms, one of which is dextrorotatory and the other lævorotatory. These two forms are mirror images and are not superimposable. Such pairs of crystals are said to be *enantiomorphous* (quartz crystals are actually hemihedral and are mirror images). X-ray analysis has shown that the quartz crystal lattice is built up of silicon and oxygen atoms arranged in left- and right-handed spirals. One is the mirror image of the other, and the two are not superimposable. When quartz crystals are fused, the optical activity is lost. Therefore the optical activity is entirely due to the *asymmetry of the crystalline structure*, since fusion brings about only a physical change. Thus we have a group of substances which are optically active only so long as they remain solid; fusion, vaporisation or solution in a solvent causes loss of optical activity.

Optical activity due to molecular structure. There are many compounds which are optically active in the solid, fused, gaseous or dissolved state, *e.g.*, glucose, tartaric acid, etc. In this case the optical activity is entirely due to the *asymmetry of the molecular structure* (see, however, §11). The original molecule and its non-superimposable mirror image are known as *enantiomorphs* (this name is taken from crystallography) or *optical antipodes*. They are also often referred to as *optical isomers*, but there is a tendency to reserve this term to denote *all* isomers which have the same structural formula but different configurations (see §1).

Properties of enantiomorphs. It appears that enantiomorphs are identical physically except in two respects:

(i) their manner of rotating polarised light; the rotations are equal but opposite.

(ii) the absorption coefficients for dextro- and lævocircularly polarised light are different; this difference is known as *circular dichroism* or the *Cotton effect* (see also §8. III).

The crystal forms of enantiomorphs may be mirror images of each other, *i.e.*, the crystals themselves may be enantiomorphous, but this is unusual [see also §10(i)]. Enantiomorphs are similar chemically, but their rates of reaction with other optically active compounds are usually different [see §10(vii)]. They may also be different physiologically, *e.g.*, (+)-histidine is sweet, (−)-tasteless; (−)-nicotine is more poisonous than (+)-.

§3. The tetrahedral carbon atom. In 1874, van't Hoff and Le Bel, independently, gave the solution to the problem of optical isomerism in organic compounds. van't Hoff proposed the theory that if the four valencies of the carbon atom are arranged tetrahedrally (not necessarily regular) with the carbon atom at the centre, then all the cases of isomerism known are accounted for. Le Bel's theory is substantially the same as van't Hoff's, but differs in that whereas van't Hoff believed that the valency distribution was definitely tetrahedral and fixed as such, Le Bel believed that the valency directions were not rigidly fixed, and did not specify the tetrahedral arrangement,

but thought that *whatever* the spatial arrangement, the molecule C*abde* would be *asymmetric*. Later work has shown that van't Hoff's theory is more in keeping with the facts (see below). Both van't Hoff's and Le Bel's theories were based on the assumption that the four hydrogen atoms in methane are equivalent; this assumption has been shown to be correct by means of chemical and physico-chemical methods. Before the tetrahedral was proposed, it was believed that the four carbon valencies were planar, with the carbon atom at the centre of a square (Kekulé, 1858).

Pasteur (1848) stated that all substances fell into two groups, those which were superimposable on their mirror images, and those which were not. In substances such as quartz, optical activity is due to the dissymmetry of the *crystal* structure, but in compounds like sucrose the optical activity is due to *molecular* dissymmetry. Since it is impossible to have molecular dissymmetry if the molecule is flat, Pasteur's work is based on the idea that molecules are three-dimensional and arranged dissymmetrically. A further interesting point in this connection is that Pasteur quoted an irregular tetrahedron as one example of a dissymmetric structure. Also, Paterno (1869) had proposed *tetrahedral models* for the structure of the isomeric compounds $C_2H_4Cl_2$ (at that time it was thought that there were three isomers with this formula; one ethylidene chloride and two ethylene chlorides).

§3a. Evidence for the tetrahedral carbon atom. The molecule CX_4 constitutes a five-point system, and since the four valencies of carbon are equivalent, their disposition in space may be assumed to be symmetrical. Thus there are three symmetrical arrangements possible for the molecule CX_4, one planar and two solid—pyramidal and tetrahedral. By comparing the number of isomers that have been prepared for a given compound with the number predicted by the above three spatial arrangements, it is possible to decide which one is correct.

Compounds of the types Ca_2b_2 *and* Ca_2bd. Both of these are similar, and so we shall only discuss molecule Ca_2b_2.

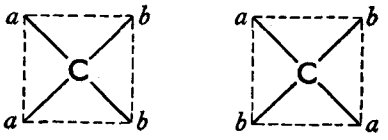


FIG. 2.1.

(i) If the molecule is planar, then *two* forms are possible (Fig. 1). This planar configuration can be either square or rectangular; in each case there are two forms only.

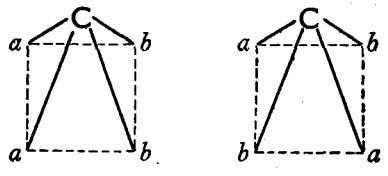


FIG. 2.2.

(ii) If the molecule is pyramidal, then *two* forms are possible (Fig. 2). There are only two forms, whether the base is square or rectangular.

(iii) If the molecule is tetrahedral, then only *one* form is possible (Fig. 3; the carbon atom is at the centre of the tetrahedron).

In practice, only one form is known for each of the compounds of the types Ca_2b_2 and Ca_2bd; this agrees with the tetrahedral configuration.

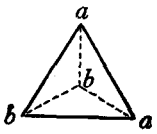


FIG. 2.3.

Compounds of the type Cabde. (i) If the molecule is planar, then *three* forms are possible (Fig. 4).

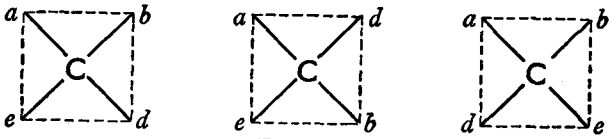


FIG. 2.4.

(ii) If the molecule is pyramidal, then *six* forms are possible; there are three pairs of enantiomorphs. Each of the forms in Fig. 4, drawn as a pyramid, is not superimposable on its mirror image, *e.g.*, Fig. 5 shows one pair of enantiomorphs.

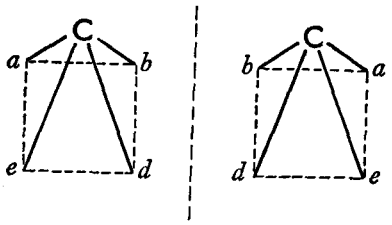


FIG. 2.5.

(iii) If the molecule is tetrahedral, there are *two* forms possible, one related to the other as object and mirror image, which are not superimposable, *i.e.*, the tetrahedral configuration gives rise to one pair of enantiomorphs (Fig. 6).

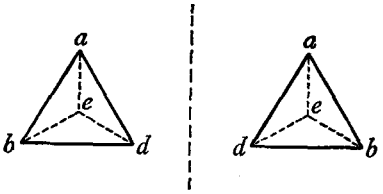


FIG. 2.6.

In practice, compounds of the type *Cabde* give rise to only one pair of enantiomorphs; this agrees with the tetrahedral configuration.

When a compound contains four different groups attached to a carbon atom, that carbon atom is said to be asymmetric (actually, of course, it is the *group* which is asymmetric; a *carbon atom* cannot be asymmetric). The majority of optically active compounds (organic) contain one or more asymmetric carbon atoms. It should be remembered, however, that the *essential* requirement for optical activity is the *asymmetry of the molecule.*

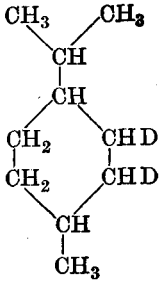
A molecule may contain two or more asymmetric carbon atoms and still not be optically active (see, *e.g.*, §7d).

A most interesting case of an optically active compound containing one asymmetric carbon atom is the resolution of *s*-butylmercuric bromide, EtMeCH·HgBr (Hughes, Ingold *et al.*, 1958). This appears to be the first example of the resolution of a simple organometallic compound where the asymmetry depends only on the carbon atom attached to the metal.

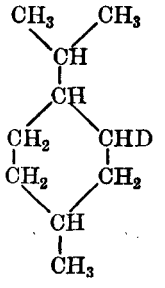
Isotopic asymmetry. In the optically active compound C*abde*, the groups *a*, *b*, *d* and *e* (which may or may not contain carbon) are all different, but two or more may be *structural* isomers, *e.g.*, propyl*iso*propylmethanol is optically active. The substitution of hydrogen by deuterium has also been investigated in recent years to ascertain whether these two atoms are sufficiently different to give rise to optical isomerism. The earlier work gave conflicting results, *e.g.*, Clemo *et al.* (1936) claimed to have obtained a small rotation for α-pentadeuterophenylbenzylamine, $C_6D_5{\cdot}CH(C_6H_5){\cdot}NH_2$, but this was disproved by Adams *et al.* (1938). Erlenmeyer *et al.* (1936) failed to resolve $C_6H_5{\cdot}CH(C_6D_5){\cdot}CO_2H$, and Ives *et al.* (1948) also failed to resolve a number of deutero-compounds, one of which was

$$C_6H_5{\cdot}CH_2{\cdot}CHD{\cdot}CO_2H.$$

More recent work, however, is definitely conclusive in favour of optical activity, *e.g.*, Eliel (1949) prepared optically active phenylmethyldeuteromethane, $CH_3{\cdot}CHD{\cdot}C_6H_5$, by reducing optically active phenylmethylmethyl chloride, $CH_3{\cdot}CHCl{\cdot}C_6H_5$, with lithium aluminium deuteride; Ross *et al.* (1956) have prepared (—)-2-deuterobutane by reduction of (—)-2-chlorobutane with lithium aluminium deuteride; and Alexander *et al.* (1949) reduced *trans*-2-*p*-menthene with deuterium (Raney nickel catalyst) and obtained a 2 : 3-dideutero-*trans*-*p*-menthane (I) that was slightly lævorotatory. Alexander (1950) also reduced (—)-menthyl toluene-*p*-sulphonate and obtained an optically active 3-deutero-*trans*-*p*-menthane (II).



I



II

Some other optically active compounds with deuterium asymmetry are, *e.g.*, (III; Streitwieser, 1955) and (IV; Levy *et al.*, 1957):

$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHDOH$ (III) $\qquad$ $CH_3{\cdot}CHDOH$ (IV)

A point of interest here is that almost all optically active deuterium compounds have been prepared from optically active precursors. Exceptions are (V) and (VI), which have been resolved by Pocker (1961).

$C_6H_5{\cdot}CHOH{\cdot}C_6D_5$ (V) $\qquad$ $C_6H_5{\cdot}CDOH{\cdot}C_6D_5$ (VI)

Further evidence for the tetrahedral carbon atom

(i) Conversion of the *two* forms (enantiomorphs) of the molecule C*abde*

into Ca_2bd results in the formation of *one* compound only (and disappearance of optical activity), *e.g.*, both dextro- and lævorotatory lactic acid may be reduced to the *same* propionic acid, which is not optically active. These results are possible only with a tetrahedral arrangement (Fig. 7; see §5 for the convention for drawing tetrahedra).

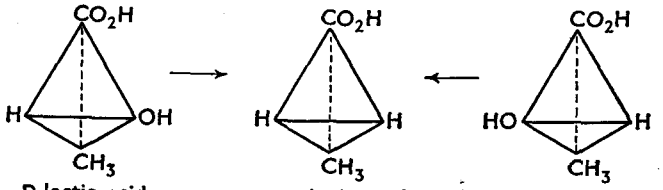


FIG. 2.7.

(ii) If the configuration is tetrahedral, then interchanging any two groups in the molecule *Cabde* will produce the enantiomorph, *e.g.*, *b* and *e* (see Fig. 8). Fischer and Brauns (1914), starting with (+)-*iso*propylmalonamic

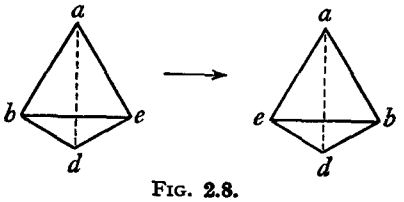
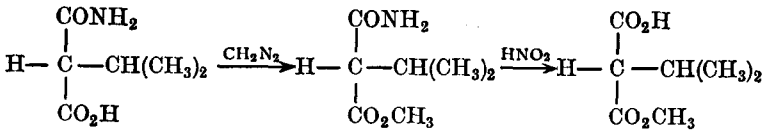
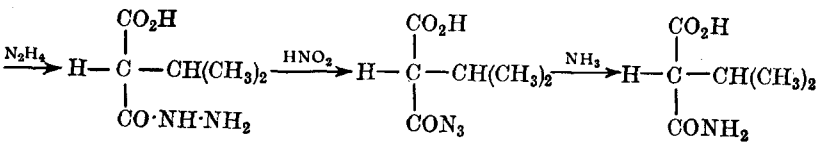


FIG. 2.8.



(+)-acid



(−)-acid

acid, carried out a series of reactions whereby the carboxyl and the carbonamide groups were interchanged; the product was (−)-*iso*propylmalonamic acid. It is most important to note that in this series of reactions no bond connected to the asymmetric carbon atom was ever broken (for an explanation, see Walden Inversion, Ch. III).

This change from one enantiomorph into the other is in agreement with the tetrahedral theory. At the same time, this series of reactions shows that optical isomers have identical structures, and so the difference must be due to the spatial arrangement.

(iii) X-ray crystallography, dipole moment measurements, absorption spectra and electron diffraction studies show that the four valencies of carbon are arranged tetrahedrally with the carbon atom inside the tetrahedron.

It should be noted in passing that the tetrahedra are not regular unless four identical groups are attached to the central carbon atom; only in this

case are the four bond lengths equal. In all other cases the bond lengths will be different, the actual values depending on the nature of the atoms joined to the carbon atom (see §15b. I).

§4. Two postulates underlie the tetrahedral theory.

(i) **The principle of constancy of the valency angle.** Mathematical calculation of the angle subtended by each side of a regular tetrahedron at the central carbon atom (Fig. 9) gives a value of 109° 28′. Originally, it was postulated (van't Hoff) that the valency angle was fixed at this value. It is now known, however, that the valency angle may deviate from this value. The four valencies of carbon are formed by hybridisation of the

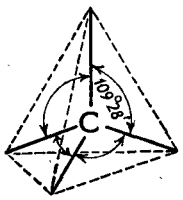


FIG. 2.9.

$2s^2$ and $2p^2$ orbitals, *i.e.*, there are four sp^3 bonds (see Vol. I, Ch. II). Quantum mechanical calculations show that the four carbon valencies in the molecule Ca_4 are equivalent and directed towards the four corners of a regular tetrahedron. Furthermore, quantum-mechanical calculations require the carbon bond angles to be close to the tetrahedral value, since change from this value is associated with loss in bond strength and consequently decrease in stability. According to Coulson *et al.* (1949), calculation has shown that the *smallest* valency angle that one can reasonably expect to find is 104°. It is this value which is found in the *cyclo*propane and *cyclo*butane rings, these molecules being relatively unstable because of the "bent" bonds (Coulson; see Baeyer Strain Theory, Vol. I, Ch. XIX).

(ii) **The principle of free rotation about a single bond.** Originally, it was believed that internal rotation about a single bond was completely free. When the thermodynamic properties were first calculated for ethane on the assumption that there was complete free rotation about the carbon–carbon single bond, the results obtained were in poor agreement with those obtained experimentally. This led Pitzer *et al.* (1936) to suggest that there

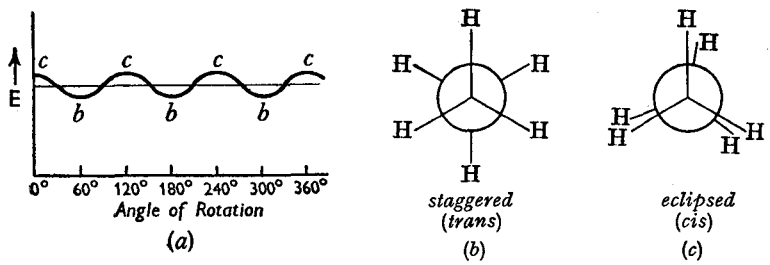


FIG. 2.10.

was restricted rotation about the single bond, and calculations on this basis gave thermodynamic properties in good agreement with the experimental ones. The potential energy curve obtained for ethane, in which one methyl group is imagined to rotate about the C—C bond as axis with the other group at rest, is shown in Fig. 10 (*a*). Had there been complete free rotation, the graph would have been a horizontal straight line. Fig. 10 (*b*) is the Newman (1952) projection formula, the carbon atom nearer to the eye

being designated by equally spaced radii and the carbon atom further from the eye by a circle with three equally spaced radial extensions. Fig. 10 (*b*) represents the *trans-* or **staggered** form in which the hydrogen atoms (on the two carbon atoms) are as far apart as possible. Fig. 10 (*c*) represents the *cis-* or **eclipsed** form in which the hydrogen atoms are as close together as possible. It can be seen from the graph that the eclipsed form has a higher potential energy than the staggered, and the actual difference has been found to be (by calculation) about 2·85 kg.cal./mole. The value of

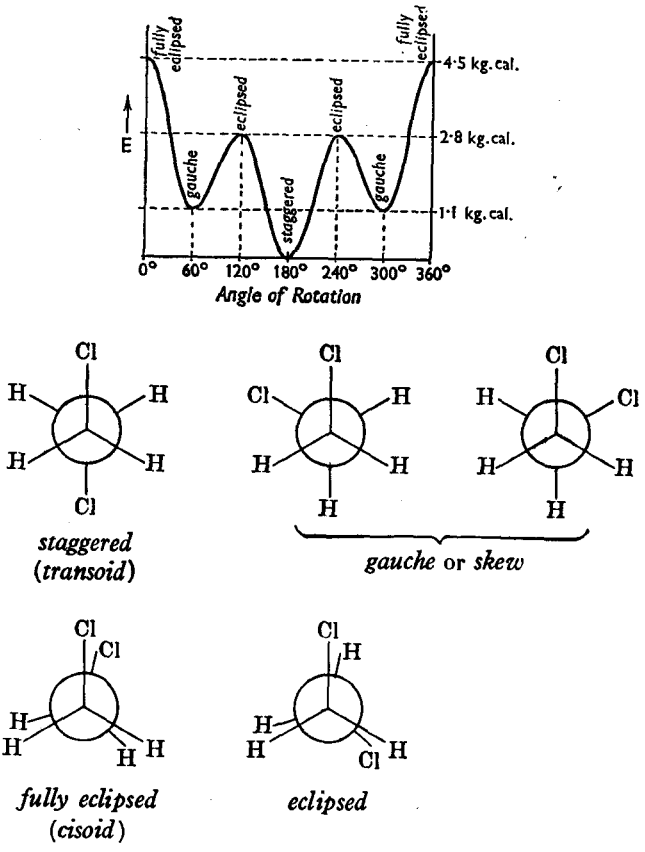


FIG. 2.11 (i).

this potential energy barrier is too low to permit the isolation of each form by chemical methods.

Now let us consider the case of ethylene chloride. According to Bernstein (1949), the potential energy of ethylene chloride undergoes the changes shown in Fig. 2.11 (i) when one CH_2Cl group is rotated about the C—C bond with the other CH_2Cl at rest. There are two positions of minimum energy, one corresponding to the staggered (transoid) form and the other to the gauche (skew) form, the latter possessing approximately 1·1 kg.cal. more than the former. The fully eclipsed (cisoid) form possesses about 4·5 kg.cal. more energy than the staggered form and thus the latter is the preferred form, *i.e.*, the molecule is largely in this form. Dipole moment studies show that this is so in practice, and also show (as do Raman spectra studies) that the ratio of the two forms varies with the temperature. Furthermore,

infra-red, Raman spectra and electron diffraction studies have shown that the gauche form is also present. According to Mizushima *et al.* (1938), only the staggered form is present at low temperatures.

The problem of internal rotation about the central C—C bond in *n*-butane is interesting, since the values of the potential energies of the various forms have been used in the study of cyclic compounds (see *cyclo*hexane, §11. IV). The various forms are shown in Fig. 2.11 (ii), and if the energy content of the staggered form is taken as zero, then the other forms have the energy contents shown (Pitzer, 1951).

From the foregoing account it can be seen that, in theory, there is no free

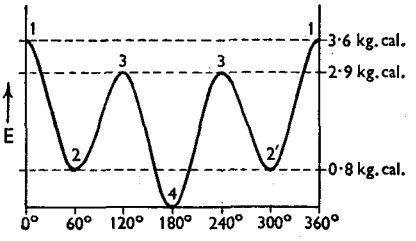
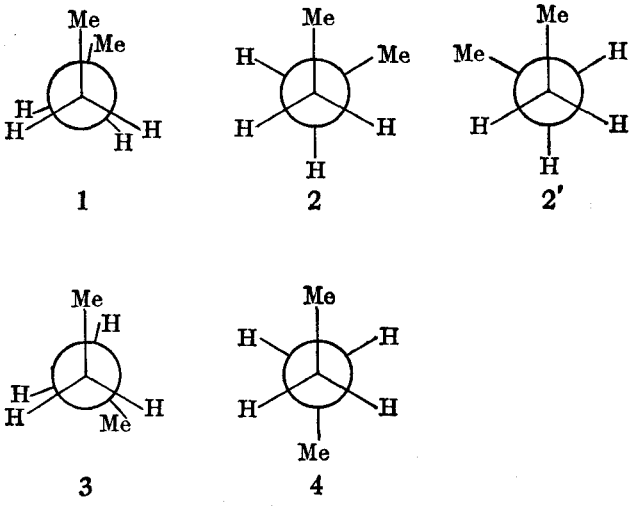


FIG. 2.11 (ii).



rotation about a single bond. In practice, however, it may occur if the potential barriers of the various forms do not differ by more than about 10 kg.cal./mole. Free rotation about a single bond is generally accepted in *simple* molecules. Restricted rotation, however, may occur when the molecule contains groups large enough to impede free rotation, *e.g.*, in *ortho*-substituted diphenyls (see Ch. V). In some cases resonance can give rise to restricted rotation about a "single" bond.

§**4a. Conformational analysis.** Molecules which can form isomers by rotation about single bonds are called **flexible molecules,** and the different forms taken up are known as different **conformations.** The terms *rotational isomers* and *constellations* have also been used in the same sense as conformations.

Various definitions have been given to the term *conformation* (which was

originally introduced by W. N. Haworth, 1929). In its widest sense, conformation has been used to describe different spatial arrangements of a molecule which are not superimposable. This means, in effect, that the terms *conformation* and *configuration* are equivalent. There is, however, an important difference in meaning between these terms. The definition of configuration, in the classical sense (§1), does not include the problem of the internal forces acting on the molecule. The term conformation, however, is the spatial arrangement of the molecule when all the internal forces acting on the molecule are taken into account. In this more restricted sense, the term conformation is used to designate different spatial arrangements arising by twisting or rotation of bonds of a *given* configuration (used in the classical sense).

The existence of potential energy barriers between the various conformations shows that there are internal forces acting on the molecule. The nature of these interactions that prevent free rotation about single bonds, however, is not completely clear. According to one theory, the hindering of internal rotation is due to dipole–dipole forces. Calculation of the dipole moment of ethylene chloride on the assumption of free rotation gave a value not in agreement with the experimental value. Thus free rotation cannot be assumed, but on the assumption that there is interaction between the two groups through dipole–dipole attractive or repulsive forces, there will be preferred conformations, *i.e.*, the internal rotation is not completely free. This restricted rotation is shown by the fact that the dipole moment of ethylene chloride increases with temperature; in the staggered form the dipole moment is zero, but as energy is absorbed by the molecule, rotation occurs to produce finally the eclipsed form in which the dipole moment is a maximum. Further work, however, has shown that factors other than dipole–dipole interactions must also be operating in opposing the rotation. One of these factors is **steric repulsion,** *i.e.*, repulsion between the nonbonded atoms (of the rotating groups) when they are brought into close proximity (*cf.* the van der Waals forces, §2. I). The existence of steric repulsion may be illustrated by the fact that although the bond moment of C—Cl is greater than that of C—Br, the energy difference between the eclipsed and staggered conformations of ethylene chloride is less than that of ethylene bromide. Furthermore, if steric repulsion does affect internal rotation, then in the ethylene halides, steric repulsion between the hydrogen and halogen atoms, if sufficiently large, will give rise to two other potential energy minima (these correspond to the two gauche forms, and these have been shown to be present; see Fig. 2.11 (i), §4).

Other factors also affect stability of the various conformations. Staggered and gauche forms always exist in molecules of the type $CH_2Y{\cdot}CH_2Z$ (where Y and Z are Cl, Br, I, CH_3, etc.), and usually the staggered form is more stable than the gauche. In a molecule such as ethylene chlorohydrin, however, it is the gauche form which is more stable than the staggered, and this is due to the fact that intramolecular hydrogen bonding is possible in the former but not in the latter.

In addition to the factors already mentioned, there appear to be other factors that cause the absence of complete free rotation about a single bond, *e.g.*, the energy barrier in ethane is too great to be accounted for by steric repulsion only. Several explanations have been offered; *e.g.*, Pauling (1958) has proposed that the energy barrier in ethane (and in similar molecules) results from repulsions between adjacent bonding pairs of electrons, *i.e.*, the bonding pairs of the C—H bonds on one carbon atom repel those on the other carbon atom. Thus the preferred conformation will be the staggered one (*cf.* §1. VI). It is still possible, however, that steric repulsion is also present, and this raises the barrier height.

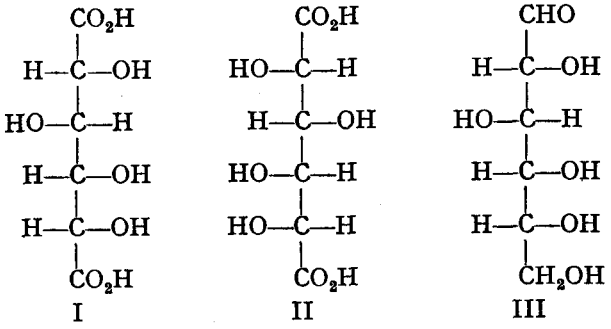
When the stability of a molecule is decreased by internal forces produced by interaction between constituent parts, that molecule is said to be under **steric strain.** There are three sources of steric strain, *i.e.*, the internal forces may arise from three different causes, *viz.*, (i) repulsion between non-bonded atoms, (ii) dipole interactions and (iii) distortion of bond-angles. Which of these plays the predominant part depends on the nature of the molecule in question. This study of the existence of preferred conformations in molecules, and the relating of physical and chemical properties of a molecule to its preferred conformation, is known as **conformational analysis.** The energy differences between the various conformations determine which one is the most stable, and the ease of transformation depends on the potential energy barriers that exist between these conformations. It should be noted that the molecule, in its *unexcited* state, will exist largely in the conformation of lowest energy content. If, however, the energy differences between the various conformations are small, then when *excited*, the molecule can take up a less favoured conformation, *e.g.*, during the course of reaction with other molecules (see §11. IV).

Because of the different environments a reactive centre may have in different conformations, conformation will therefore affect the course and rate of reactions involving this centre (see §11. IV).

Many methods are now used to investigate the conformation of molecules, *e.g.*, thermodynamic calculations, dipole moments, electron and X-ray diffraction, infra-red and Raman spectra, rotatory dispersion, NMR and chemical methods.

§5. **Conventions used in stereochemistry.** The original method of indicating enantiomorphs was to prefix each one by *d* or *l* according as it was dextrorotatory or lævorotatory. van't Hoff (1874) introduced a + and − notation for designating the configuration of an asymmetric carbon atom. He used mechanical models (built of tetrahedra), and the + and − signs were given by observing the tetrahedra of the mechanical model from the centre of the model. Thus a molecule of the type *Cabd·Cabd* may be designated + +, − −, and + −. E. Fischer (1891) pointed out that this + and − notation can lead to wrong interpretations when applied to molecules containing more than two asymmetric carbon atoms (the signs given to each asymmetric carbon atom depend on the point of observation in the molecule). Fischer therefore proposed the use of plane projection diagrams of the mechanical models instead of the + and − system.

Fischer, working on the configurations of the sugars (see §1. VII), obtained the plane formulæ I and II for the enantiomorphs of saccharic acid, and



arbitrarily chose I for dextrorotatory saccharic acid, and called it *d*-saccharic acid. He then, from this, deduced formula III for *d*-glucose. Furthermore, Fischer thought it was more important to indicate stereo-

chemical relationships than merely to indicate the actual direction of rotation. He therefore proposed that the **prefixes *d* and *l* should refer to stereochemical relationships and not to the direction of rotation of the compound.** For this scheme to be self-consistent (among the sugars) it is necessary to choose *one* sugar as standard and then refer all the others to it. Fischer apparently intended to use the scheme whereby the compounds derived from *a given aldehyde sugar* should be designated according to the *direction of rotation of the parent aldose.*

Natural mannose is dextrorotatory. Hence natural mannose will be *d*-mannose, and all derivatives of *d*-mannose, *e.g.*, mannonic acid, mannitol, mannose phenylhydrazone, etc., will thus belong to the *d*-series. Natural glucose is dextrorotatory. Hence natural glucose will be *d*-glucose, and all its derivatives will belong to the *d*-series. Furthermore, Fischer (1890) converted natural mannose into natural glucose as follows:

$$d\text{-mannose} \longrightarrow d\text{-mannonic acid} \longrightarrow d\text{-mannolactone} \longrightarrow d\text{-glucose}$$

Since natural glucose is *d*-glucose (according to Fischer's scheme), the prefix *d* for natural glucose *happens* to agree with its dextrorotation (with *d*-mannose as standard). Natural fructose can also be prepared from natural mannose (or natural glucose), and so will be *d*-fructose. Natural fructose, however, is lævorotatory, and so is written as *d*(−)-fructose, the symbol *d* indicating its *stereochemical* relationship to the parent aldose glucose, and the symbol − placed in parentheses before the name indicating the *actual direction of rotation.*

More recently the symbols *d* and *l* have been replaced by D and L for configurational relationships, *e.g.*, L(+)-lactic acid. Also, when dealing with compounds that cannot be referred to an arbitrarily chosen standard, (+)- and (−)- are used to indicate the sign of the rotation. The prefixes *dextro* and *lævo* (without hyphens) are also used.

Fischer's proposal to use *each aldose* as the arbitrary standard for its derivatives leads to some difficulties, *e.g.*, natural arabinose is dextrorotatory, and so is to be designated D-arabinose. Now natural arabinose (D-arabinose) can be converted into mannonic acid which, if D-arabinose is taken as the parent aldose, will therefore be D-mannonic acid. This same acid, however, can also be obtained from L-mannose, and so should be designated as L-mannonic acid. Thus in cases such as this the use of the symbol D or L will depend on the *historical order* in which the stereochemical relationships were established. This, obviously, is an unsatisfactory position, which was realised by Rosanoff (1906), who showed that if the enantiomorphs of glyceraldehyde (a molecule which contains only *one* asymmetric carbon atom) are chosen as the (arbitrary) standard, then a satisfactory system for correlating stereochemical relationships can be developed. He also proposed that the formula of dextrorotatory glyceraldehyde should be written as in Fig. 12 (*c*), in order that the arrangement of its asymmetric carbon atom should agree with the arrangement of C_5 in Fischer's projection formula for natural glucose (see formula III above).

It is of great interest to note in this connection that in 1906 the active forms of glyceraldehyde had not been isolated, but in 1914 Wohl and Momber separated DL-glyceraldehyde into its enantiomorphs, and in 1917 they showed that dextrorotatory glyceraldehyde was stereochemically related to natural glucose, *i.e.*, with D(+)-glyceraldehyde as arbitrary standard, natural glucose is D(+)-glucose (see §1. VII).

The accepted convention for drawing D(+)-glyceraldehyde—the agreed (*arbitrary*) standard—is shown in Fig. 12 (*a*). The tetrahedron is drawn so that three corners are imagined to be *above* the plane of the paper, and the fourth *below* the plane of the paper. Furthermore, the spatial arrangement

of the four groups joined to the central carbon atom *must be placed as shown in Fig.* 12 (*a*), *i.e.*, **the accepted convention for drawing** D(+)-**glyceraldehyde places the hydrogen atom at the left and the hydroxyl group at the right, with the aldehyde group at the top corner.** Now imagine the tetrahedron to rotate about the horizontal line joining H and OH until it takes up the position shown in Fig. 12 (*b*). This is the *conventional* position for a tetrahedron, groups joined to *full horizontal* lines

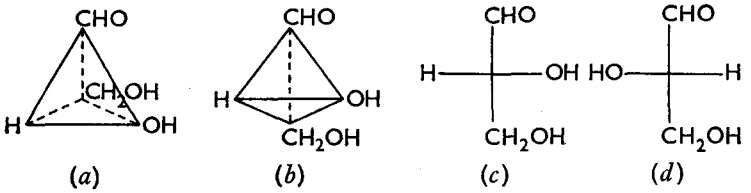
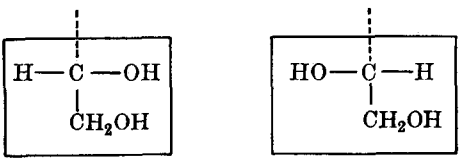


FIG. 2.12.

being *above* the plane of the paper, and those joined to *broken vertical* lines being *below* the plane of the paper. The *conventional plane-diagram* is obtained by drawing the full horizontal and broken vertical lines of Fig. 12 (*b*) as full lines, placing the groups as they appear in Fig. 12 (*b*), and taking the asymmetric carbon atom to be at the point where the lines cross. Although Fig. 12 (*c*) is a plane-diagram, it is most important to remember that horizontal lines represent groups above the plane, and vertical lines groups below the plane of the paper. Many authors prefer to draw Fig. 12 (*c*) [and Fig. 12 (*d*)] with a *broken* vertical line. Fig. 12 (*d*) represents the plane-diagram formula of L(−)-glyceraldehyde; here *the hydrogen atom is to the right and the hydroxyl group to the left.* Thus any compound that can be prepared from, or converted into, D(+)-glyceraldehyde will belong to the D-series. Similarly, any compound that can be prepared from, or converted into, L(−)-glyceraldehyde will belong to the L-series. When representing relative configurational relationship of molecules containing more than one asymmetric carbon atom, *the asymmetric carbon atom of glyceraldehyde is always drawn at the bottom,* the rest of the molecule being built up from this unit.

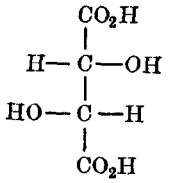


D-series L-series

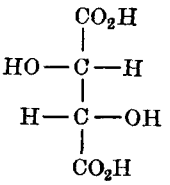
Thus we have a scheme of classification of *relative* configurations based on D(+)-glyceraldehyde as *arbitrary* standard. Even on this basis confusion is still possible in relating configurations to the standard (see later).

Until recently there was no way of determining, with certainty, the *absolute* configuration of molecules. *Arbitrary choice* makes the configuration of D(+)-glyceraldehyde have the hydrogen to the left and the hydroxyl to the right. Bijvoet *et al.* (1951), however, have shown by X-ray analysis of sodium rubidium tartrate that it is possible to differentiate between the two optically active forms, *i.e.*, it is possible to determine the *absolute* configuration of these two enantiomorphs. These authors showed that natural dextrorotatory tartaric acid has the configuration assigned to it by Fischer (who correlated its configuration with that of the saccharic acids). The configurations of the tartaric acids are a troublesome problem. Fischer

wrote the configuration of natural dextrorotatory tartaric acid as IV. If we use the convention of writing the glyceraldehyde unit at the bottom,

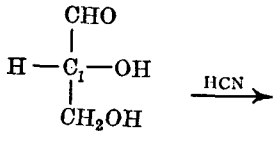


IV

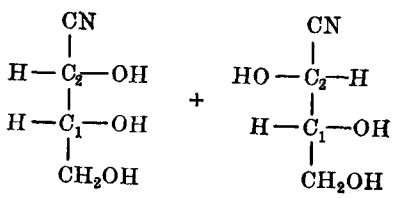


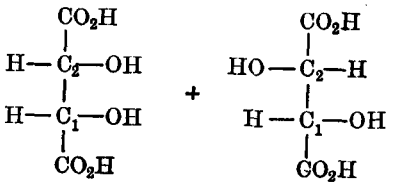
V

then IV is L(+)-tartaric acid and V D(−)-tartaric acid. This relationship (to glyceraldehyde) is confirmed by the conversion of D(+)-glyceraldehyde



D(+)-glyceraldehyde

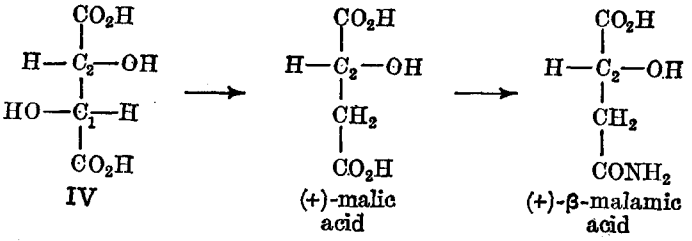




*meso*tartaric acid

(−)-tartaric acid

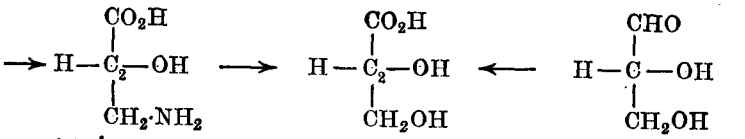
into lævorotatory tartaric acid *via* the Kiliani reaction (see Vol. I). Thus (−)-tartaric acid is D(−)-tartaric acid (V). On the other hand, (+)-tartaric acid can be converted into D(−)-glyceric acid, and so (+)-tartaric acid is D(+)-tartaric acid (IV). In this reduction of (+)-tartaric acid to (+)-malic



IV

(+)-malic acid

(+)-β-malamic acid

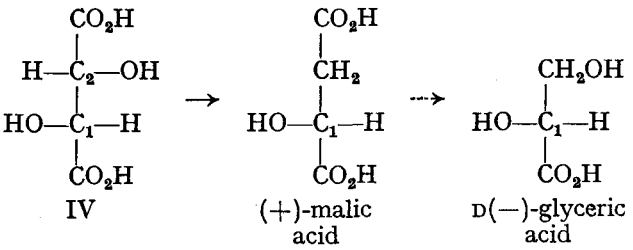


(+)-*iso*serine

D(−)-glyceric acid

D(+)-glyceraldehyde

acid (by hydriodic acid), it has been *assumed* that it is C_1 which has been reduced, *i.e.*, in *this* case the configuration of C_2 has been correlated with glyceraldehyde and not that of C_1 as in the previous set of reactions. Had, however, C_2 been reduced, then the final result would have been (+)-tartaric acid *still through the intermediate*, (+)-*malic acid* (two exchanges of groups give the same malic acid as before). Since (+)-malic acid has been correlated



with (+)-glyceraldehyde (see §9a), (+)-tartaric acid should be designated D(+)-tartaric acid. The designation L(+)-tartaric acid is used by those chemists who regard this acid as a carbohydrate derivative (see also §5a).

§5a. Correlation of configurations. As we have seen (§5), since the relative configurations of (+)-tartaric acid and (+)-glyceraldehyde have been established, it is now possible to assign *absolute* configurations to many compounds whose relative configurations to (+)-glyceraldehyde are known, since the configurations assigned to them are actually the absolute configurations. The methods used for correlating configurations are:

(i) Chemical reactions without displacement at the asymmetric centre concerned (see §5b).

(ii) Chemical reactions with displacement at the asymmetric centre concerned (see the Walden inversion, §§3, 4. III).

(iii) X-ray analysis (see §5).

(iv) Asymmetric inductive correlation (see asymmetric synthesis, §7. III).

(v) Optical rotations: (*a*) Monochromatic rotations (see, *e.g.*, carbohydrates, §6. VII; steroids, §4b. XI). (*b*) Rotatory dispersion (see steroids, §4b. XI).

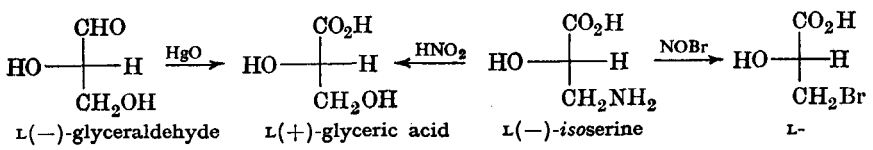
(vi) The study of quasi-racemic compounds (see §9a).

(vii) Enzyme studies.

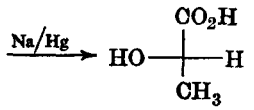
§5b. Correlation of configurations without displacement at the asymmetric centre concerned. Since no bond joined to the asymmetric centre is ever broken, this method is an extremely valuable method of correlation. Before discussing examples, the following point is worth noting. For amino-acids, natural (−)-serine, $CH_2OH{\cdot}CH(NH_2){\cdot}CO_2H$, was chosen as the arbitrary standard. Thus correlation with glyceraldehyde was indicated by D_g or L_g, and with serine by D_s or L_s. These two standards have now been correlated, and it has been shown that $L_g \equiv L_s$, *i.e.*, natural (−)-serine belongs to the L-series (with glyceraldehyde as absolute standard; see also §4. XIII).

The following examples illustrate this method of correlation.

(i)



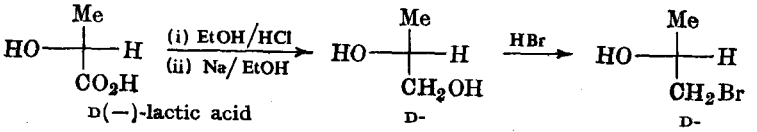
L(−)-glyceraldehyde L(+)-glyceric acid L(−)-*iso*serine L-



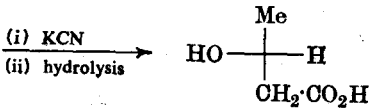
L(+)-lactic acid

It can be seen from this example that change in the sign of rotation does not necessarily indicate a change in configuration.

(ii)

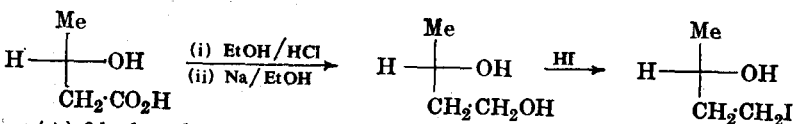


D(−)-lactic acid D- D-

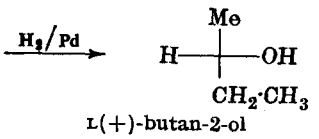


D(−)-β-hydroxybutyric acid

(iii)



L(+)-β-hydroxybutyric acid L- L-



L(+)-butan-2-ol

(iv) Another example is that in the terpene series (see §23e. VIII).

§5c. Specification of asymmetric configurations. Cahn, Ingold and Prelog (1956) have produced a scheme for the specification of absolute configurations. Let us consider the procedure for a molecule containing one asymmetric carbon atom.

(i) The four groups are first ordered according to the **sequence rule.** According to this rule, the groups are arranged in *decreasing atomic number* of the atoms by which they are bound to the asymmetric carbon atom. If two or more of these atoms have the same atomic number, then the relative priority of the groups is determined by a similar comparison of the atomic numbers of the *next* atoms in the groups (*i.e.*, the atoms joined to the atom joined to the asymmetric carbon atom). If this fails, then the next atoms of the groups are considered. Thus one works *outwards* from the asymmetric carbon atom until a selection can be made for the sequence of the groups.

(ii) Next is determined whether the sequence describes a right- or left-handed pattern on the molecular model as viewed according to the **conversion rule.** When the four groups in the molecule C*abcd* have been ordered in the priority *a*, *b*, *c*, *d*, the conversion rule states that their spatial pattern shall be described as right- or left-handed according as the sequence $a \rightarrow b \rightarrow c$ is clockwise or anticlockwise when viewed from an external point on the side *remote* from *d* (the group with the lowest priority), *e.g.*, (I) in Fig. 13 shows a right-handed (*i.e.*, clockwise) arrangement.

(iii) Absolute configuration labels are then assigned. The asymmetry leading under the sequence and conversion rules to a right- and left-handed

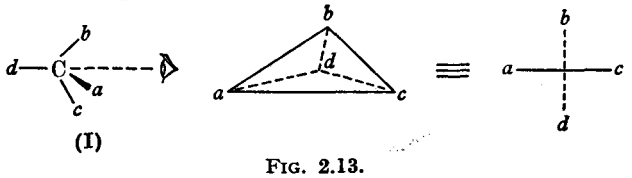
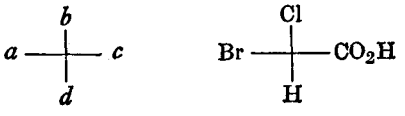


FIG. 2.13.

pattern is indicated by *R* and *S* respectively (*R*; *rectus*, right: *S*; *sinister*, left).

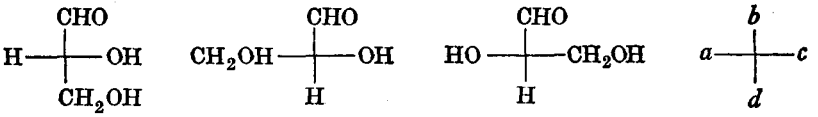
Let us first consider bromochloroacetic acid (II). The priority of the groups according to the sequence rule is Br (*a*), Cl (*b*), CO_2H (*c*) and H (*d*).



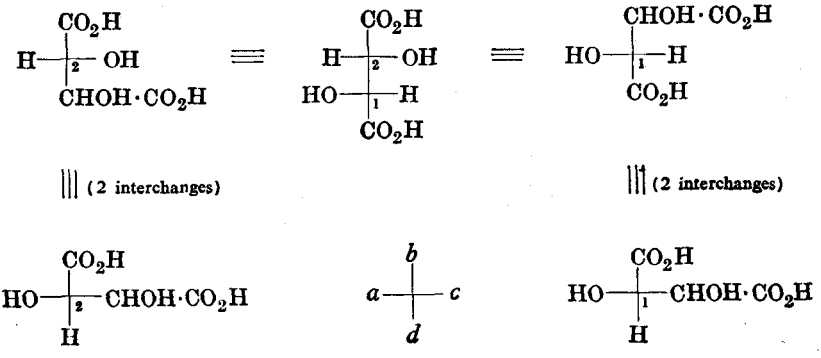
(II)

Hence by the conversion rule, (II) is the (*R*)-form ($a \rightarrow b \rightarrow c$ is clockwise).

Now let us consider D(+)-glyceraldehyde. By *convention* it is drawn as III (this is also the *absolute* configuration). Oxygen has the highest priority

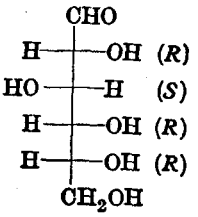


and H the lowest. Thus OH is *a* and H is *d*. Since both the CHO and CH_2OH groups are attached to the asymmetric carbon by carbon, it is necessary to determine the priorities of these two groups by working outwards. The C of the CHO is bound to (H, O=) and that of the CH_2OH to (H, H, OH). When a double or triple bond is present in the group, the atom at the remote end of the multiple bond is regarded as duplicated or triplicated, respectively. Thus the double-bonded oxygen atom gives higher priority to the CHO group (≡H, O, O). Hence CHO is *b* and CH_2OH is *c*. Since the interchanging of two groups inverts the configuration, the sequence (III) → (IV) → (V) gives the *original* configuration. Since (V) corresponds to (VI), it thus follows that D(+)-glyceraldehyde is (*R*)-glyceraldehyde.



When a molecule contains two or more asymmetric carbon atoms, each asymmetric carbon atom is assigned a configuration according to the sequence and conversion rules and is then specified with *R* or *S*, *e.g.*, (+)-tartaric acid. Thus the absolute configuration of (+)-tartaric acid is (*RR*)-tartaric acid [this clearly indicates the relationship between (+)-tartaric acid and D(+)-glyceraldehyde].

In a similar way it can be demonstrated that D(+)-glucose has the absolute configuration shown.



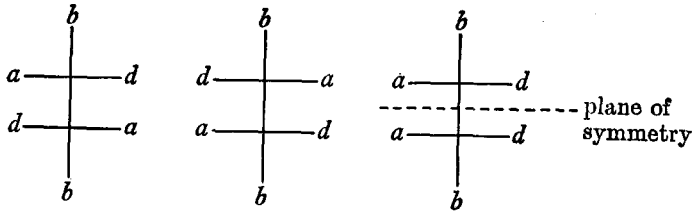
D(+)-glucose

The system has also been extended to include asymmetric molecules which have no asymmetric carbon atoms, *e.g.*, spirans, diphenyls, etc.

§6. Elements of symmetry. The test of superimposing a formula (tetrahedral) on its mirror image definitely indicates whether the molecule is symmetrical or not; it is asymmetric if the two forms are not superimposable. The most satisfactory way in which superimposability may be ascertained is to build up models of the molecule and its mirror image. Usually this is not convenient, and so, in practice, one determines whether the molecule possesses (i) a plane of symmetry, (ii) a centre of symmetry or (iii) an alternating axis of symmetry. If the molecule contains at least one of these elements of symmetry, the molecule is symmetrical; if none of these elements of symmetry is present, the molecule is asymmetric.

It should be remembered that it is the Fischer projection formula that is normally used for inspection. As pointed out in §2, it is necessary, when dealing with conformations, to ascertain whether at least one of them has one or more elements of symmetry. If such a conformation can be drawn, then the compound is *not* optically active.

(i) A **plane of symmetry** divides a molecule in such a way that points (atoms or groups of atoms) on the one side of the plane form mirror images of those on the other side. This test may be applied to both solid (tetrahedral) and plane-diagram formulæ, *e.g.*, the plane-formula of the *meso*-form of *Cabd*·*Cabd* possesses a plane of symmetry; the other two, (+) and (−), do not



(ii) A **centre of symmetry** is a point from which lines, when drawn on one side and produced an equal distance on the other side, will meet exactly similar points in the molecule. This test can be satisfactorily applied only

to three-dimensional formulæ, particularly those of ring systems, *e.g.*, 2 : 4-dimethyl*cyclo*butane-1 : 3-dicarboxylic acid (Fig. 14). The form shown possesses a centre of symmetry which is the centre of the ring. This form is therefore optically inactive.

Another example we shall consider here is that of dimethyldiketopiperazine; this molecule can exist in two geometrical isomeric forms, *cis* and

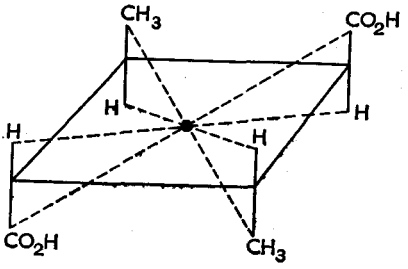
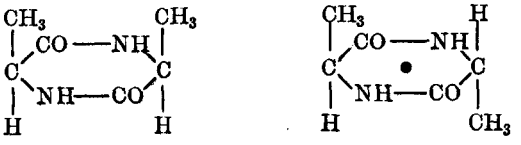


FIG. 2.14.

trans (see also §11. IV). The *cis*-isomer has no elements of symmetry and can therefore exist in two enantiomorphous forms; both are known. The *trans*-isomer has a centre of symmetry and is therefore optically inactive.



cis *trans*

It is important to note that only *even-membered* rings can possibly possess a centre of symmetry.

(iii) **Alternating axis of symmetry.** A molecule possesses an *n*-fold alternating axis of symmetry if, when rotated through an angle of $360°/n$ about this axis and then followed by reflection in a plane perpendicular to the axis, the molecule is the same as it was in the starting position. Let us consider the molecule shown in Fig. 15 (*a*) [1 : 2 : 3 : 4-tetramethyl*cyclo*butane]. This contains a four-fold alternating axis of symmetry. Rota-

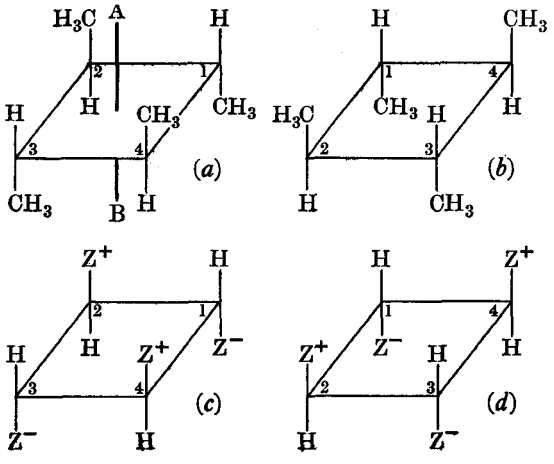
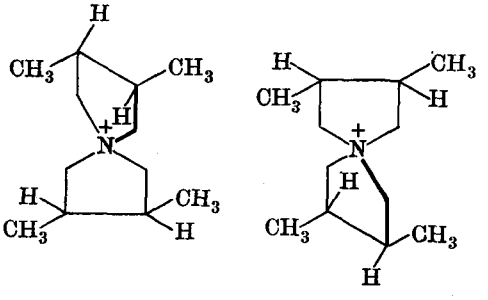


FIG. 2.15.

tion of (*a*) through 90° about axis AB which passes through the centre of the ring perpendicular to its plane gives (*b*), and reflection of (*b*) in the plane of the ring gives (*a*). It also happens that this molecule possesses two vertical planes of symmetry (through each diagonal of the ring), but if the methyl groups are replaced alternately by the asymmetric groups (+)—$CH(CH_3)\cdot C_2H_5$ and (−)—$CH(CH_3)\cdot C_2H_5$, represented by Z^+ and Z^- respectively, the resulting molecule (Fig. 15*c*) now has no planes of symmetry. Nevertheless, this molecule is *not* optically active since it does possess a four-fold alternating axis of symmetry [reflection of (*d*) (which is produced by rotation of (*c*) through 90° about the vertical axis) in the plane of the ring gives (*c*); it should be remembered that the reflection of a (+)-form is the (−)-form].

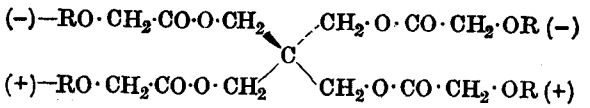
The *cyclo*butane derivative (*c*) given above to illustrate the meaning of an alternating axis of symmetry is an imaginary molecule. No compound was known in which the optical inactivity was due to the existence of *only*



I II

an alternating axis until McCasland and Proskow (1956) prepared such a molecule for the first time. This is a spiro-type of molecule (§7. V), *viz.*, 3 : 4 : 3′ : 4′-tetramethylspiro-(1 : 1′)-dipyrrolidinium *p*-toluenesulphonate, I (the *p*-toluenesulphonate ion has been omitted). This molecule is discussed in some detail in §2a. VI, but here we shall examine it for its alternating axis of symmetry. Molecule I is superimposable on its mirror image and hence is not optically active. It does not contain a plane or centre of symmetry, but it does contain a four-fold alternating axis of symmetry. To show the presence of this axis, if I rotated through 90° about the co-axis of both rings, II is obtained. Reflection of II through the central plane (*i.e.*, through the N atom) perpendicular to this axis gives a molecule identical and coincident with I.

McCasland *et al.* (1959) have now prepared a second compound, a pentaerythritol ester, whose optical inactivity can be attributed *only* to the presence of a four-fold alternating axis of symmetry (R = menthyl radical; see §16. VIII):



In practice one decides whether a molecule is symmetrical or not by looking only for a plane or centre of symmetry, since no *natural* compound has yet been found to have an alternating axis of symmetry. The presence of two or more asymmetric carbon atoms will definitely give rise to optical isomerism, but nevertheless *some* isomers may not be optically active because these ***molecules as a whole*** are not asymmetric (see §7d).

§7. The number of isomers in optically active compounds. The number of optical isomers that can theoretically be derived from a molecule containing one or more asymmetric carbon atoms is of fundamental importance in stereochemistry.

§7a. Compounds containing one asymmetric carbon atom. With the molecule *Cabde* only two optical isomers are possible, and these are related as object and mirror image, *i.e.*, there is one pair of enantiomorphs, *e.g.*, D- and L-lactic acid. If we examine an *equimolecular* mixture of dextrorotatory and lævorotatory lactic acids, we shall find that the mixture is optically inactive. This is to be expected, since enantiomorphs have equal but opposite rotatory power. Such a mixture (of equimolecular amounts) is said to be **optically inactive by external compensation,** and is known as a **racemic modification** (see also §9). A compound which is optically inactive by external compensation is known as the **racemic compound** and is designated as *r*-, (±)- or DL-, *e.g.*, *r*-tartaric acid, (±)-limonene, DL-lactic acid.

Thus a compound containing *one* asymmetric carbon atom can exist in *three* forms: (+)-, (−) and (±).

Conversion of molecule Ca_2bd *into* Cabde. Let us consider as an example the bromination of propionic acid to give α-bromopropionic acid.

$$CH_3{\cdot}CH_2{\cdot}CO_2H \xrightarrow{Br_2/P} CH_3{\cdot}CHBr{\cdot}CO_2H$$

II and III (Fig. 16) are enantiomorphs, and since molecule I is symmetrical about its vertical axis, it can be anticipated from the theory of probability

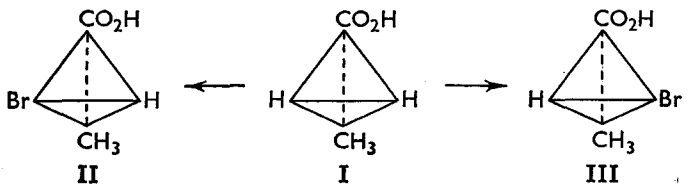


FIG. 2.16.

that either hydrogen atom should be replaced equally well to give (±)-α-bromopropionic acid. This actually does occur in practice.

§7b. Compounds containing two different asymmetric carbon atoms. When we examine the molecule *Cabd·Cabe*, *e.g.*, α : β-dibromobutyric acid, $CH_3{\cdot}CHBr{\cdot}CHBr{\cdot}CO_2H$, we find that there are *four* possible spatial arrangements for this type of molecule (Fig. 17). I and II are enantiomorphs (the configurations of *both* asymmetric carbon are reversed),

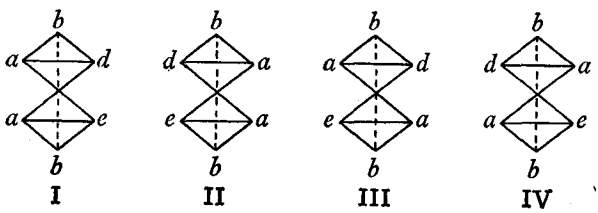


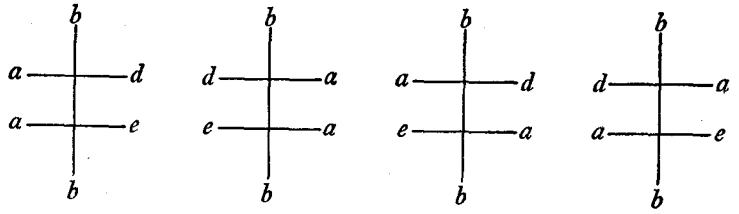
FIG. 2.17.

and an equimolecular mixture of them forms a racemic modification; similarly for III and IV. Thus there are six forms in all for a compound of the type *Cabd·Cabe*: two pairs of enantiomorphs and two racemic modifications.

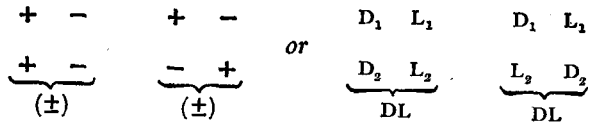
I and III are not identical in configuration and are not mirror images

(the configuration of *one* of the two asymmetric carbon atoms is reversed); they are known as **diastereoisomers,** *i.e.*, they are optical isomers but not enantiomorphs (mirror images). Diastereoisomers differ in physical properties such as melting point, density, solubility, dielectric constant and specific rotation. Chemically they are similar, but their rates of reaction with other optically active compounds are different (*cf.* the properties of enantiomorphs, §2).

The plane-diagrams of molecules I–IV (Fig. 17) will be V–VIII, respectively, as shown. It should be remembered that groups joined to horizontal lines lie above the plane of the paper, and those joined to vertical lines lie below the plane of the paper (§5).



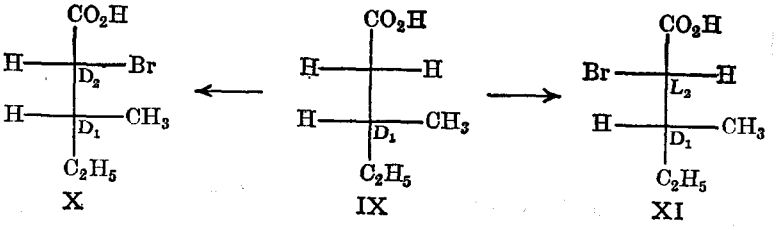
Instead of writing down all the possible configurations, the number of optical isomers for a compound of the type *Cabd*·*Cabe* may be obtained by indicating the *configuration* of each asymmetric carbon atom by the symbol + or −, or by D or L; thus:



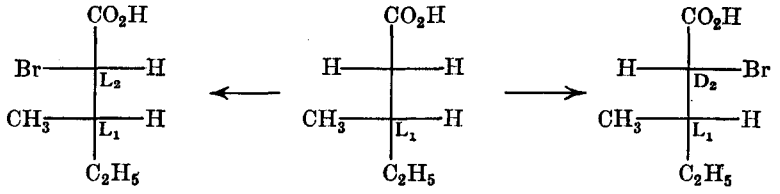
Conversion of molecule Ca_2b·*Cabe into Cabd*·*Cabe.* Let us consider the bromination of β-methylvaleric acid to give α-bromo-β-methylvaleric acid.

$$CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CH_2{\cdot}CO_2H \xrightarrow{Br_2/P} CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CHBr{\cdot}CO_2H$$

β-Methylvaleric acid contains *one* asymmetric carbon atom, but the bromine derivative contains *two*. Let us first consider the case where the configuration of the asymmetric carbon atom in the starting material is D_1 (IX). Bromination of this will produce molecules X and XI; these are diastereoisomers and are produced in *unequal* amounts. This is to be anticipated; the two α-hydrogen atoms are not symmetrically placed with respect to the lower half of the molecule, and consequently different rates of substitution can be expected. In the same way, bromination of the starting material in which the configuration of the asymmetric carbon atom is L_1 (XII) leads to the formation of a mixture of diastereoisomers (XIII and XIV) in unequal amounts. One can expect, however, that the amount of XIII produced from XII would be the same as that of X from IX since,



in both cases, the positions of the bromine atoms with respect to the methyl group are the same. Similarly, the amount of XIV from XII will be the same as that of XI from IX. Thus bromination of (±)-β-methylvaleric



XIII XII XIV

acid will result in a mixture of four bromo derivatives which will consist of two racemic modifications in unequal amounts, and the mixture will be optically inactive.

§7c. Compounds containing three different asymmetric carbon atoms. A molecule of this type is *Cabd·Cab·Cabe, e.g.*, the pentoses, and the number of optical isomers possible is *eight* (four pairs of enantiomorphs):

D_1 L_1	D_1 L_1	D_1 L_1	L_1 D_1
D_2 L_2	D_2 L_2	L_2 D_2	D_2 L_2
D_3 L_3	L_3 D_3	D_3 L_3	D_3 L_3
DL	DL	DL	DL

All the cases discussed so far are examples of a series of compounds which contain *n structurally distinct* carbon atoms, *i.e.*, they belong to the series *Cabd·*$(Cab)_{n-2}$*·Cabe.* In general, if there are *n* asymmetric carbon atoms in the molecule (of this series), then there will be 2^n optically active forms and 2^{n-1} resolvable forms (*i.e.*, 2^{n-1} pairs of enantiomorphs). These formulæ also apply to *monocyclic* compounds containing *n* different asymmetric carbon atoms; they may or may not apply to *fused ring systems* since spatial factors may play a part in the possible existence of various configurations (see, *e.g.*, camphor, §23a. VIII).

§7d. Compounds of the type *Cabd·*$(Cab)_x$*·Cabd.* In compounds of this type the two *terminal* asymmetric carbon atoms are *similar*, and the number of optically active forms possible depends on whether *x* is *odd* or *even.*

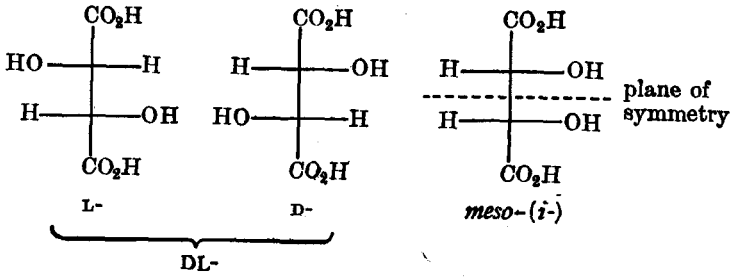
(i) EVEN SERIES

(*a*) *Cabd·Cabd, e.g.*, tartaric acid. In a compound of this type the rotatory power of each asymmetric carbon atom is the same. Now let us consider the number of optical isomers possible.

D	L	D	L
D	L	L	D
I	II	III	IV

In molecules I and II, the upper and lower halves reinforce each other; hence I, as a whole, has the dextro- and II, the lævo-configuration, *i.e.*, I and II are optically active, and enantiomorphous. On the other hand, in III the two halves are in opposition, and so the molecule, *as a whole*, will not show optical activity. It is also obvious that III and IV are identical, *i.e.*, there is only *one* optically inactive form of *Cabd·Cabd.* Molecule III is said to be **optically inactive by internal compensation.** Molecule III

is known as the ***meso***-form, and is a diastereoisomer of the pair of enantiomorphs I and II. The *meso*-form is also known as the *inactive* form and is represented as the *i*-form; **the *meso*-form cannot be resolved** (see also §10). Thus there are four forms possible for the molecule *Cabd*·*Cabd*: one pair of enantiomorphs, one racemic modification and one *meso*- (*i*-) form. These forms for tartaric acid are:



Inspection of these formulæ shows that the D- and L- forms do not possess any elements of symmetry; the *meso*-form, however, possesses a plane of symmetry.

(*b*) *Cabd*·*Cab*·*Cab*·*Cabd*, *e.g.*, saccharic acid,

$$CO_2H{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CHOH{\cdot}CO_2H.$$

The rotatory powers of the two terminal asymmetric carbon atoms are the same, and so are those of the middle two (the rotatory powers of the latter are almost certainly different from those of the former; equality would be fortuitous). The possible optical isomers are as follows (V–XIV):

V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
D_1	L_1	D_1	L_1	D_1	L_1	D_1	L_1	D_1	D_1
D_2	L_2	L_2	D_2	D_2	L_2	D_2	L_2	D_2	L_2
D_2	L_2	L_2	D_2	D_2	L_2	L_2	D_2	L_2	D_2
D_1	L_1	D_1	L_1	L_1	D_1	D_1	L_1	L_1	L_1
DL		DL		DL		DL		*meso*-forms	

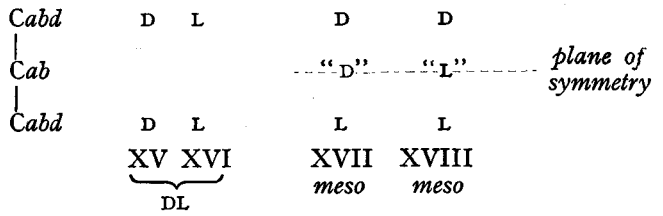
Molecules V and VI are optically active (enantiomorphous) and are not "internally compensated"; VII and VIII are optically active (enantiomorphous) and are not "internally compensated"; IX and X are optically active (enantiomorphous) but are "internally compensated at the ends"; XI and XII are optically active (enantiomorphous) but are "internally compensated in the middle"; XIII and XIV are *meso*-forms and are optically inactive by (complete) internal compensation. Thus there are eight optically active forms (four pairs of enantiomorphs), and two *meso*-forms.

In general, in the series of the type *Cabd*·$(Cab)_{n-2}$·*Cabd*, if n is the number of asymmetric carbon atoms and n is *even*, then there will be 2^{n-1} optically active forms, and $2^{\frac{n-2}{2}}$ *meso*-forms.

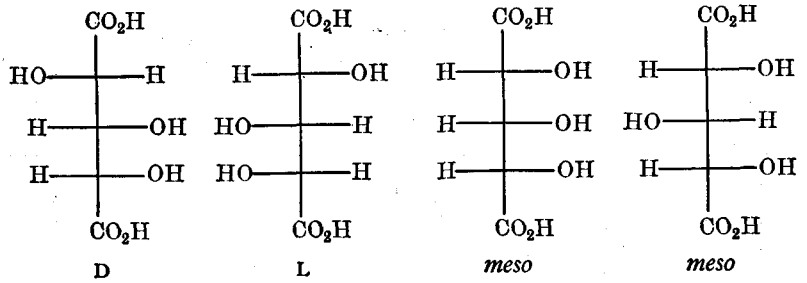
(ii) ODD SERIES

(*a*) *Cabd*·*Cab*·*Cabd*, *e.g.*, trihydroxyglutaric acid. If the two terminal asymmetric carbon atoms have the same configuration, then the central carbon atom has two identical groups joined to it and hence cannot be asymmetric. If the two terminal configurations are opposite, then the central carbon atom has apparently four different groups attached to it

(the two ends are mirror images and not superimposable). Thus the central carbon atom becomes asymmetric, but at the same time the two terminal atoms "compensate internally" to make the *molecule as a whole* symmetrical (there is now a plane of symmetry), and consequently the compound is not optically active. In this molecule the central carbon atom

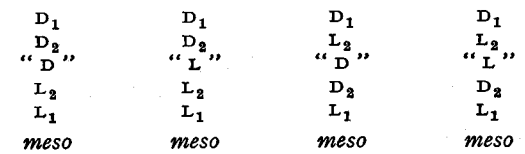


is said to be *pseudo-asymmetric,* and is designated "D" and "L" (or ⊕ and ⊖ if the + and − convention is used; §7b). There will, however, be *two meso*-forms since the pseudo-asymmetric carbon atom can have two different configurations (see XV–XVIII). Thus there are five forms in all: two optically active forms (enantiomorphs), one racemic modification, and two *meso*-forms. The following are the corresponding trihydroxyglutaric acids, all of which are known.

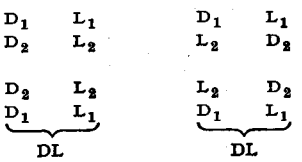


(*b*) *Cabd·Cab·Cab·Cab·Cabd.* In this molecule the central carbon atom is pseudo-asymmetric when the left-hand side of the molecule has the opposite configuration to that of the right-hand side; the central carbon atom is symmetrical when both sides have the same configuration. In all other cases the central carbon atom is asymmetric, the molecule now containing five asymmetric carbon atoms. The following table shows that there are *sixteen* optical isomers possible, of which twelve are optically active (six pairs of enantiomorphs), and four are *meso*-forms.

Ends with opposite configurations



Ends with the same configurations



Molecule with five asymmetric carbon atoms

D_1	L_1	D_1	L_1	D_1	L_1	D_1	L_1
D_2	L_2	D_2	L_2	D_2	L_2	D_2	L_2
D	L	L	D	D	L	L	D
D_2	L_2	D_2	L_2	L_2	D_2	L_2	D_2
L_1	D_1	L_1	D_1	D_1	L_1	D_1	L_1
DL		DL		DL		DL	

In general, in the series of the type $Cabd{\cdot}(Cab)_{n-2}{\cdot}Cabd$, if n is the number of " asymmetric " carbon atoms and n is *odd*, then there will be 2^{n-1} optical isomers, of which $2^{\frac{n-1}{2}}$ are *meso*-forms and the remainder optically active forms.

§8. The racemic modification. The racemic modification is an equimolecular mixture of a pair of enantiomorphs, and it may be prepared in several ways.

(i) Mixing of equimolecular proportions of enantiomorphs produces the racemic modification.

(ii) Synthesis of asymmetric compounds from symmetrical compounds always results in the formation of the racemic modification. This statement is true only if the reaction is carried out in the absence of other optically active compounds or circularly polarised light (see asymmetric synthesis, §7. III).

(iii) **Racemisation.** The process of converting an optically active compound into the racemic modification is known as racemisation. The (+)- and (−)-forms of most compounds are capable of racemisation under the influence of heat, light, or chemical reagents. Which agent is used depends on the nature of the compound, and at the same time the ease of racemisation also depends on the nature of the compound, *e.g.*,

(*a*) Some compounds racemise so easily that they cannot be isolated in the optically active forms.

(*b*) A number of compounds racemise spontaneously when isolated in optically active forms.

(*c*) The majority of compounds racemise with various degrees of ease under the influence of different reagents.

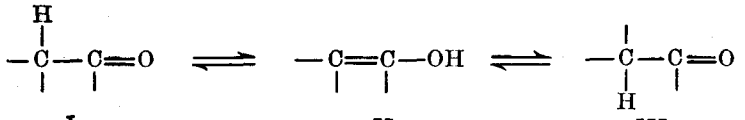
(*d*) A relatively small number of compounds cannot be racemised at all.

When a molecule contains two or more asymmetric carbon atoms and the configuration of only *one* of these is inverted by some reaction, the process is then called *epimerisation.*

Many theories have been proposed to explain racemisation, but owing to the diverse nature of the structures of the various optically active compounds, one cannot expect to find *one* theory which would explain the racemisation of *all types* of optically active compounds. Thus we find that a number of mechanisms have been suggested, each one explaining the racemisation of a particular type of compound.

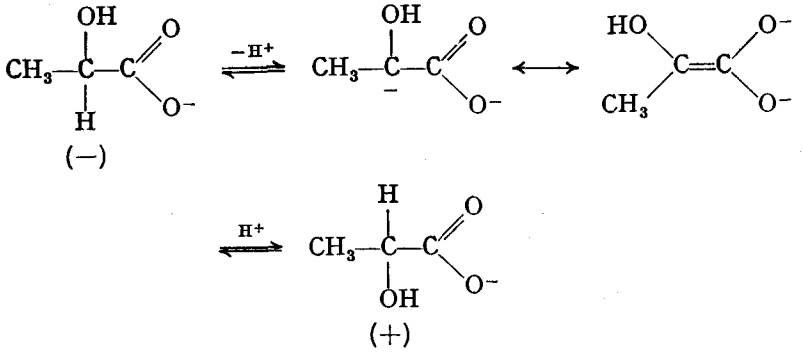
A number of compounds which are easily racemisable are those in which the asymmetric carbon atom is joined to a hydrogen atom and a negative group. Since this type of compound can undergo tautomeric change, the mechanism proposed for this racemisation is one *via* enolisation. When the intermediate enol-form, which is symmetrical, reverts to the keto-form, it can do so equally well to produce the (+)- or (−)-forms, *i.e.*, the compound will racemise. Let us consider the case of keto-enol tautomerism: In the keto-form, I, the carbon joined to the hydrogen atom and the oxo group is asymmetric; in the enol-form, II, this carbon atom has lost its asymmetry. When the enol-form reverts to the keto-form, it can do so to produce the original keto molecule I, but owing to its symmetry, the

enol-form can produce equally well the keto-form III in which the configuration of the asymmetric carbon atom is opposite to that in I. Thus racemisation, according to this scheme, occurs *via* the enol-form, *e.g.*, (—)-lactic acid



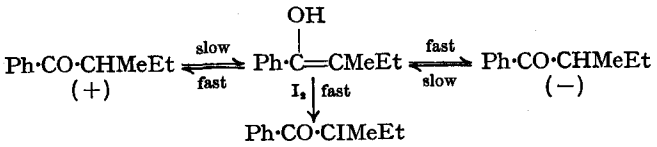
I II III

is racemised in aqueous sodium hydroxide, and this change may be formulated:

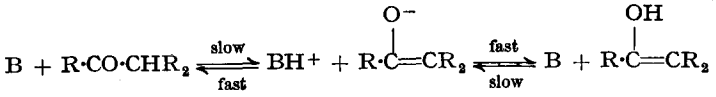


There is a great deal of evidence to support this tautomeric mechanism. When the hydrogen atom joined to the asymmetric carbon atom is replaced by some group that prevents tautomerism (enolisation) then racemisation is also prevented (at least under the same conditions as the original compound), *e.g.*, mandelic acid, $C_6H_5{\cdot}CHOH{\cdot}CO_2H$, is readily racemised by warming with aqueous sodium hydroxide. On the other hand, atrolactic acid, $C_6H_5{\cdot}C(CH_3)(OH){\cdot}CO_2H$, is not racemised under the same conditions; in this case keto-enol tautomerism is no longer possible.

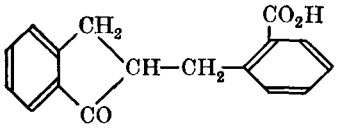
Racemisation of compounds capable of exhibiting keto-enol tautomerism is catalysed by acids and bases. Since keto-enol tautomerism is also catalysed by acids and bases, then if racemisation proceeds *via* enolisation, the rates of racemisation and enolisation should be the same. This relationship has been established by means of kinetic studies, *e.g.*, Bartlett *et al.* (1935) found that the rate of acid-catalysed iodination of 2-butyl phenyl ketone was the same as that of racemisation in acid solution. This is in keeping with both reactions involving the rate-controlling formation of the enol (see Vol. I, Ch. X):



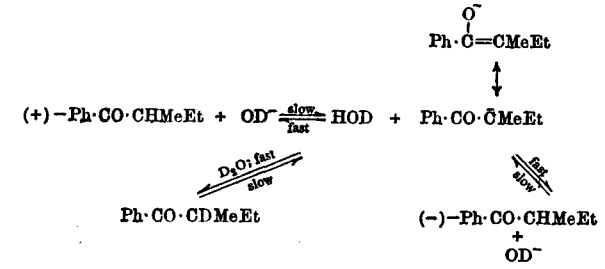
On the other hand, on the basis that the rate-determining step in base-catalysed enolisation and racemisation is the formation of the enolate ion, then the two processes will also occur at the same rate.



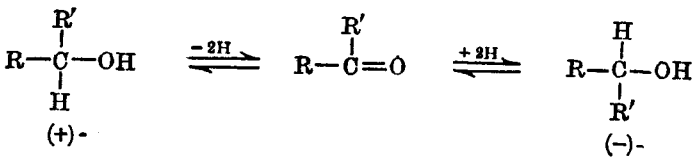
Hsü *et al.* (1936) found that the rates of bromination and racemisation (in the presence of acetate ions) of 2-*o*-carboxybenzyl-1-indanone were identical.



Further support for this mechanism is the work of Ingold *et al.* (1938) who showed that the rate of racemisation of (+)-2-butyl phenyl ketone in dioxan-deuterium oxide solution in the presence of NaOD is the same as the rate of deuterium exchange. This is in keeping with the formation of the enolate ion (or carbanion), which is common to both reactions.



There are many compounds containing an asymmetric carbon atom which can be racemised under suitable conditions although there is no possibility of tautomerism. A number of different types of compounds fall into this group, and the mechanism proposed for racemisation depends on the type of compound under consideration. In the case of compounds of the type of (—)-limonene (§13. VIII), which is racemised by strong heating, the mechanisms proposed are highly speculative (see, for example, Werner's theory, §4. V). A number of optically active secondary alcohols can be racemised by heating with a sodium alkoxide. This has been explained by a reversible dehydrogenation (Hückel, 1931) and there is some evidence to support this mechanism (Doering *et al.*, 1947, 1949).



Another different type of compound which can be readily racemised is that represented by α-chloroethylbenzene. When the (+)- or (—)-form is dissolved in liquid sulphur dioxide, spontaneous racemisation occurs. This has been explained by assuming ionisation into a carbonium ion (Polanyi *et al.*, 1933).

$$\underset{(+)\text{-}}{C_6H_5\cdot CHCl\cdot CH_3} \rightleftharpoons C_6H_5\cdot \overset{+}{C}H\cdot CH_3 + Cl^- \rightleftharpoons \underset{(-)\text{-}}{C_6H_5\cdot CHCl\cdot CH_3}$$

The carbonium ion is planar (the positively charged carbon atom is probably in a state of trigonal hybridisation) and consequently symmetrical; recombination with the chlorine ion can occur equally well to form the (+)- and (—)-forms, *i.e.*, racemisation occurs. The basis of this mechanism is that alkyl halides in liquid sulphur dioxide exhibit an electrical conductivity, which has been taken as indicating ionisation. Hughes, Ingold

et al. (1936), however, found that pure α-chloroethylbenzene in pure liquid sulphur dioxide does not conduct, but when there is conduction, then styrene and hydrogen chloride are present. These authors showed that under the conditions of purity, the addition of bromine leads to a quantitative yield of styrene dibromide.

Polanyi showed that the rate of racemisation of α-chloroethylbenzene in liquid sulphur dioxide is unaffected by added chloride ions. Hughes and Ingold suggest that the rate of racemisation is accounted for by the rate of formation of hydrogen chloride; thus:

$$C_6H_5{\cdot}CHCl{\cdot}CH_3 \xrightarrow{\text{slow}} C_6H_5{\cdot}\overset{+}{C}H{\cdot}CH_3 + Cl^-$$

$$C_6H_5{\cdot}\overset{+}{C}H{\cdot}CH_3 \xrightarrow{\text{fast}} C_6H_5{\cdot}CH = CH_2 + H^+$$

It is the recombination of the styrene with the hydrogen chloride that produces the racemised product; this may be written as follows

$$\underset{(+)\text{-}}{C_6H_5{\cdot}CHCl{\cdot}CH_3} \rightleftharpoons C_6H_5{\cdot}CH = CH_2 + HCl \rightleftharpoons \underset{(-)\text{-}}{C_6H_5{\cdot}CHCl{\cdot}CH_3}$$

The racemisation of optically active hydrocarbons containing a tertiary hydrogen atom is very interesting. It has been shown that such hydrocarbons undergo hydrogen exchange when dissolved in concentrated sulphuric acid (Ingold *et al.*, 1936), and the mechanism is believed to occur *via* a carbonium ion (Burwell *et al.*, 1948).

$$R_3CH + 2H_2SO_4 \longrightarrow R_3C^+ + HSO_4^- + SO_2 + 2H_2O$$

$$R_3C^+ + R_3CH \longrightarrow R_3CH + R_3C^+, \text{ etc.}$$

This reaction is very useful for racemising optically active hydrocarbons, *e.g.*, Burwell *et al.* (1948) racemised optically active 3-methylheptane in concentrated sulphuric acid (the carbonium ion is flat):

$$\underset{(+)\text{-}}{C_2H_5{-}\overset{CH_3}{\overset{|}{C}}H{-}C_4H_9} + C_2H_5{-}\overset{CH_3}{\overset{|}{C}}{}^+{-}C_4H_9 \longrightarrow C_2H_5{-}\overset{CH_3}{\overset{|}{C}}{}^+{-}C_4H_9 + \underset{(\pm)\text{-}}{C_2H_5{-}\overset{CH_3}{\overset{|}{C}}H{-}C_4H_9}$$

The racemisation of other types of optically active compounds is described later (see diphenyl compounds, §4. V; nitrogen compounds, §2a. VI; phosphorus compounds, §3b. VI; arsenic compounds, §4a. VI).

§9. **Properties of the racemic modification.** The racemic modification may exist in three different forms in the solid state.

(i) **Racemic mixture.** This is also known as a **(±)-conglomerate,** and is a mechanical mixture of two types of crystals, the (+)- and (−)-forms; there are two phases present. The physical properties of the racemic mixture are mainly the same as those of its constituent enantiomorphs. The most important difference is the m.p. (see §9a).

(ii) **Racemic compound.** This consists of a pair of enantiomorphs in combination as a molecular compound; only one solid phase is present. The physical properties of a racemic compound are different from those of the constituent enantiomorphs, but in solution racemic compounds dissociate into the (+)- and (−)-forms.

(iii) **Racemic solid solution.** This is also known as a ***pseudo*-racemic compound,** and is a solid solution (one phase system) formed by a pair of enantiomorphs crystallising together due to their being isomorphous. The

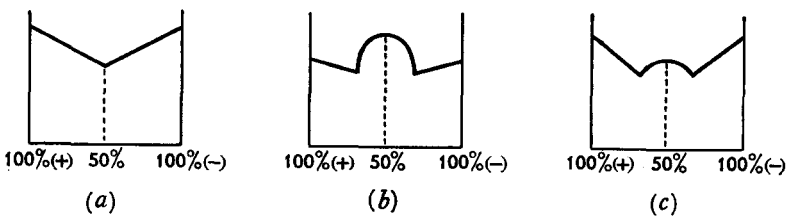
properties of the racemic solid solution are mainly the same as those of its constituent enantiomorphs; the m.p.s may differ (see §9a).

§9a. Methods for determining the nature of a racemic modification. One simple method of examination is to estimate the amounts of water of crystallisation in the enantiomorphs (only one need be examined) and in the racemic modification; if these are different, then the racemic modification is a racemic compound. Another simple method is to measure the densities of the enantiomorphs and the racemic modification; again, if these are different, the racemic modification is a racemic compound; *e.g.*, tartaric acids.

	D-Tartaric acid	L-Tartaric acid	Racemic Tartaric acid
Melting point . . .	170°	170°	206°
Water of crystallisation .	None	None	$1H_2O$
Density	1·7598	1·7598	1·697
Solubility in H_2O (at 20°)	139 g./100 ml.	139 g./100 ml.	20·6 g./100 ml.

There are, however, two main methods for determining the nature of a racemic modification: a study of the freezing-point curves and a study of the solubility curves (Roozeboom, 1899; Andriani, 1900).

Freezing-point curves. These are obtained by measuring the melting points of mixtures containing different amounts of the racemic modification and its corresponding enantiomorphs. Various types of curves are possible according to the nature of the racemic modification. In Fig. 18 (*a*) the



(*a*) (*b*) (*c*)

FIG. 2.18.

melting points of all mixtures are higher than that of the racemic modification alone. In this case the racemic modification is a racemic mixture (a eutectic mixture is formed at the point of 50 per cent. composition of each enantiomorph), and so addition of either enantiomorph to a racemic mixture *raises* the melting point of the latter; (±)-pinene is an example of this type. In Fig. 18 (*b*) and (*c*) the melting points of the mixtures are lower than the melting point of the racemic modification which, therefore, is a racemic compound. The melting point of the racemic compound may be above that of each enantiomorph (Fig. 18 *b*) or below (Fig. 18 *c*); in either case the melting point is *lowered* when the racemic compound is mixed with an enantiomorph; an example of Fig. 18 (*b*) is methyl tartrate, and one of Fig. 18 (*c*) is mandelic acid.

When the racemic modification is a racemic solid solution, three types of curves are possible (Fig. 19). In Fig. 19 (*a*) the freezing-point curve is a horizontal straight line, all possible compositions having the same melting point, *e.g.*, (+)- and (−)-camphor. In Fig. 19 (*b*) the freezing-point curve shows a maximum, *e.g.*, (+)- and (−)-carvoxime; and in Fig. 19 (*c*) the freezing-point curve shows a minimum, *e.g.*, (+)- and (−)-*iso*pentyl (*iso*-amyl) carbamate.

In a number of cases there is a transition temperature at which one form of the racemic modification changes into another form, *e.g.*, (±)-camphoroxime crystallises as the racemic solid solution above 103°, whereas below this temperature it is the racemic compound that is obtained [see also §10(i)].

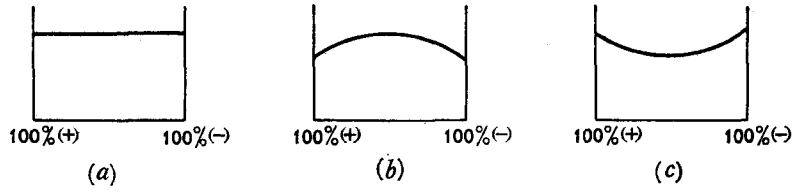
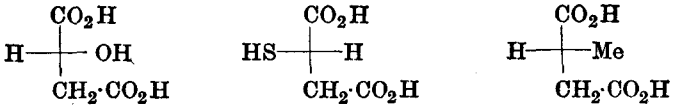


FIG. 2.19.

Fredga (1944) has introduced the study of quasi-racemic compounds as a means of correlating configurations (§5). Quasi-racemic compounds are equimolecular compounds that are formed from two optically active compounds which have *closely similar structures but opposite configurations, e.g.*,

I II

I and II. The formation of a quasi-racemic compound is detected by studying the melting-point curves of the two components. The curves obtained are similar to those of the racemic modification shown in Fig. 18 (*a*), 18 (*b*) and 19 (*a*), but with the quasi-racemic compounds these curves are unsymmetrical (since the m.p.s of the components will be different). An unsymmetrical curve 18 (*a*) indicates a eutectic mixture, an unsymmetrical 19 (*a*) a solid solution and an unsymmetrical 18 (*b*) a quasi-racemic compound. Curves for quasi-racemic compounds are given only by compounds (containing one asymmetric carbon atom) which have closely similar structures but opposite configurations. On the other hand, curves of the other two types are given by compounds of *like* configuration (but some cases are known where the configurations have been opposite). Various examples of this method of correlating configurations have now been described, *e.g.*, Fredga (1941) showed (partly by chemical methods and partly by using the quasi-racemate method) that (+)-malic acid (III) and (−)-mercaptosuccinic

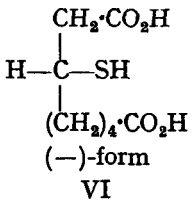


III IV V

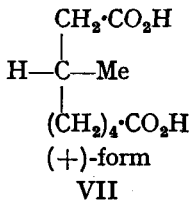
acid (IV) had opposite configurations. He then showed (1942) that (−)-mercaptosuccinic acid formed a quasi-racemic compound with (+)-methylsuccinic acid (V). Therefore (IV) and (V) have *opposite* configurations and consequently (+)-malic acid and (+)-methylsuccinic acid have the *same* configuration (see also §§10(vi) and 23e. VIII).

Mislow *et al.* (1956) have applied the m.p. curves in a somewhat different manner. They worked with 3-mercapto-octanedioic acid (VI) and 3-methyloctanedioic acid (VII). These authors found that compounds (−)-VI and (+)-VII gave solid solutions for all mixtures (unsymmetrical 19 *a*), whereas (+)-VI and (+)-VII gave a diagram with a single eutectic (unsymmetrical

18 *a*). These results indicate that (−)-VI and (+)-VII are of the same



(−)-form
VI



(+)-form
VII

absolute configuration, whereas (+)-VI and (+)-VII are of opposite configurations.

Solubility curves. The interpretation of solubility curves is difficult, but in practice the following simple scheme based on solubility may be used. A small amount of one of the enantiomorphs is added to a *saturated* solution of the racemic modification, and the resulting solution is then examined in a polarimeter. If the solution exhibits a rotation, then the racemic modification is a compound, but if the solution has a zero rotation, then the racemic modification is a mixture or a solid solution. The reasons for this behaviour are as follows. If the racemic modification is a mixture or a solid solution, then the solution (in some solvent) is saturated with respect to each enantiomorph and consequently cannot dissolve any of the added enantiomorph. If, however, the racemic modification is a compound, then the solution (in a solvent) is saturated with respect to the compound form but not with respect to either enantiomorph; hence the latter will dissolve when added and thereby produce a rotation. It should be noted that this simple method does not permit a differentiation to be made between a racemic mixture and a racemic solid solution.

Infra-red spectroscopy is also being used to distinguish a racemic compound from a racemic mixture or a racemic solid solution. In the latter the spectra are identical, but are different in the former. These observations are also true for X-ray powder diagrams, and so X-ray analysis in the solid state may also be used.

§10. Resolution of racemic modifications. Resolution is the process whereby a racemic modification is separated into its two enantiomorphs. In practice the separation may be far from quantitative, and in some cases only one form may be obtained. A large variety of methods for resolution have now been developed, and the method used in a particular case depends largely on the chemical nature of the compound under consideration.

(i) **Mechanical separation.** This method is also known as **spontaneous resolution,** and was introduced by Pasteur (1848). It depends on the crystallisation of the two forms separately, which are then separated by hand. The method is applicable only to a few cases, and then only for racemic *mixtures* where the *crystal* forms of the enantiomorphs are themselves enantiomorphous (§2). Pasteur separated sodium ammonium racemate in this way. The transition temperature of sodium ammonium racemate is 28°; above this temperature the racemic compound crystallises out, and below this temperature the racemic mixture. Now Pasteur crystallised his sodium ammonium racemate from a concentrated solution at room temperature, which must have been below 28° since had the temperature been above this he would have obtained the racemic compound, which cannot be separated mechanically. Actually, Staedel (1878) failed to repeat Pasteur's separation since he worked at a temperature above 28°.

(ii) **Preferential crystallisation by inoculation.** A super-saturated solution of the racemic modification is treated with a crystal of one enantiomorph (or an isomorphous substance), whereupon this form is precipitated.

The resolution of glutamic acid by inoculation has been perfected for industrial use (Ogawa *et al.*, 1957; Oeda, 1961). Harada *et al.* (1962) have also resolved the copper complex of DL-aspartic acid by inoculation.

(iii) **Biochemical separation** (Pasteur, 1858). Certain bacteria and moulds, when they grow in a dilute solution of a racemic modification, destroy one enantiomorph more rapidly than the other, *e.g.*, *Penicillium glaucum* (a mould), when grown in a solution of ammonium racemate, attacks the D-form and leaves the L-.

This biochemical method of separation has some disadvantages:

(*a*) Dilute solutions must be used, and so the amounts obtained will be small.

(*b*) One form is always destroyed and the other form is not always obtained in 50 per cent. yield since some of this may also be destroyed.

(*c*) It is necessary to find a micro-organism which will attack only one of the enantiomorphs.

(iv) **Conversion into diastereoisomers** (Pasteur, 1858). This method, which is the best of all the methods of resolution, consists in converting the enantiomorphs of a racemic modification into diastereoisomers (§7b); the racemic modification is treated with an optically active substance and the diastereoisomers thereby produced are separated by fractional crystallisation. Thus racemic acids may be separated by optically active bases, and *vice versa*, *e.g.*,

$$(D_{acid} + L_{acid}) + 2D_{base} \longrightarrow (D_{acid}D_{base}) + (L_{acid}D_{base})$$

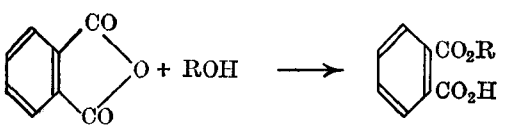
These two diastereoisomers may then be separated by fractional crystallisation and the acids (enantiomorphs) regenerated by hydrolysis with inorganic acids or with alkalis. In practice it is usually easy to obtain the less-soluble isomer in a pure state, but it may be very difficult to obtain the more-soluble isomer. In a number of cases this second (more-soluble) isomer may be obtained by preparing it in the form of *another* diastereoisomer which is less soluble than that of its enantiomorph.

Resolution by means of diastereoisomer formation may be used for a variety of compounds, *e.g.*,

(*a*) *Acids.* The optically active bases used are mainly alkaloids: brucine, quinine, strychnine, cinchonine, cinchonidine and morphine. Recently, optically active benzimidazoles (§3a. XII) have been used (Hudson *et al.*, 1939).

(*b*) *Bases.* Many optically active acids have been used, *e.g.*, tartaric acid, camphor-β-sulphonic acid and particularly α-bromocamphor-π-sulphonic acid (see §23a. VIII).

(*c*) *Alcohols.* These are converted into the acid ester derivative using either succinic or phthalic anhydride (Pickard and Kenyon, 1912). The acid ester, consisting of equimolecular amounts of the (+)- and (−)-forms,



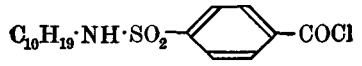
may now be resolved as for acids. Racemic alcohols may also be resolved by diastereoisomer formation with optically active acyl chlorides (to form esters) or with optically active *iso*cyanates (to form urethans):

$$RO{\cdot}CH_2{\cdot}COCl + R'OH \longrightarrow RO{\cdot}CH_2{\cdot}CO_2R' + HCl$$

$$R{\cdot}NCO + R'OH \longrightarrow R{\cdot}NH{\cdot}CO_2R'$$

In these equations R is the (−)-menthyl radical (§16. VIII); recently

N-(−)-menthyl-*p*-sulphamylbenzoyl chloride, I, has been used (Mills *et al.*, 1950).



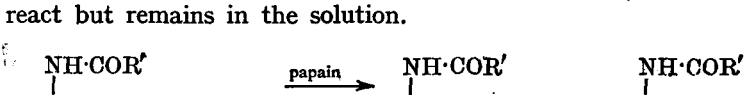
I

(*d*) *Aldehydes and Ketones.* These have been resolved by means of optically active hydrazines, *e.g.*, (−)-menthylhydrazine. Sugars have been resolved with (+)-*iso*pentanethiol (*cf.* §1. VII). Nerdel *et al.* (1952) have resolved oxo compounds with D-tartramide acid hydrazide,

$$NH_2{\cdot}CO{\cdot}CHOH{\cdot}CHOH{\cdot}CO{\cdot}NH{\cdot}NH_2;$$

this forms diastereoisomeric tartramazones.

(*e*) *Amino-compounds.* These may be resolved by conversion into diastereoisomeric anils by means of optically active aldehydes. α-Amino-acids have been resolved by preparing the acyl derivative with an optically active acyl chloride, *e.g.*, (−)-menthoxyacetyl chloride (*cf. alcohols*). Another method of resolving DL-amino-acids is asymmetric enzymic synthesis (§7. III). The racemic amino-acid is converted into the acyl derivative which is then allowed to react with aniline in the presence of the enzyme papain at the proper *p*H (Albertson, 1951). Under these conditions only the L-amino-acid derivative reacts to form an insoluble anilide; the D-acid does not react but remains in the solution.



Amino-acids have also been resolved by other means (see §4. XIII).

Asymmetric transformation. Resolution of racemic modifications by means of salt formation (the diastereoisomers are salts; *cf. acids* and *bases*) may be complicated by the phenomenon of *asymmetric transformation.* This phenomenon is exhibited by compounds that are optically unstable, *i.e.*, the enantiomorphs are readily interconvertible

$$(+)\text{-C} \rightleftharpoons (-)\text{-C}$$

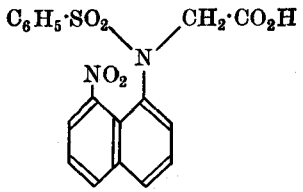
There are two types of asymmetric transformation, first order and second order. These were originally defined by Kuhn (1932), but were later redefined by Jamison and Turner (1942).

Suppose we have an optically stable (+)-base (one equivalent) dissolved in some solvent, and this is then treated with one equivalent of an optically unstable (±)-acid. At the moment of mixing, the solution will contain equal amounts of [(+)-Base·(+)-Acid] and [(+)-Base·(−)-Acid]; but since the acid is optically unstable, the two diastereoisomers will be present in unequal amounts when equilibrium is attained.

$$[(+)\text{-Base}{\cdot}(+)\text{-Acid}] \rightleftharpoons [(+)\text{-Base}{\cdot}(-)\text{-Acid}]$$

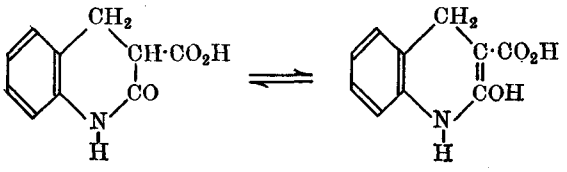
According to Jamison and Turner, first-order asymmetric transformation is the establishment of equilibrium *in solution* between the two diastereoisomers which must have a *real* existence. In second-order asymmetric transformation it is necessary that one salt should crystallise from solution; the two diastereoisomers need not have a real existence in solution. In second-order asymmetric transformation it is possible to get a complete conversion of the acid into the form that crystallises; the form may be the (+)- or (−)-, and which one it is depends on the nature of the base and the solvent.

Many examples of first- and second-order asymmetric transformation are known, and a large number of these compounds are those which owe their asymmetry to restricted rotation about a single bond (see Ch. V), *e.g.*, Mills and Elliott (1928) tried to resolve *N*-benzenesulphonyl-8-nitro-1-naphthylglycine, II, by means of the brucine salt. These authors found that either



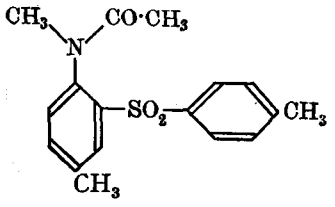
II

diastereoisomer could be obtained in approximately 100 per cent. yield by crystallisation from methanol and acetone, respectively. Another example of second-order asymmetric transformation is hydrocarbostyril-3-carboxylic acid. This compound contains an asymmetric carbon atom, and Leuchs



(1921), attempting to resolve it with quinidine, isolated approximately 90 per cent. of the (+)-form. Optical instability in this case is due to keto-enol tautomerism (*cf.* §8).

A very interesting example of second-order asymmetric transformation is 2-acetomethylamido-4′ : 5-dimethylphenylsulphone, III. When this com-



III

pound was crystallised from a supersaturated solution in ethyl (+)-tartrate, the crystals obtained had a rotation of +0·2°; evaporation of the mother liquor gave crystals with a rotation of −0·15° (Buchanan *et al.*, 1950).

(v) Another method of resolution that has been tried is the conversion of the enantiomorphs into *volatile* diastereoisomers, which are then separated by fractional distillation. So far, the method does not appear to be very successful, only a partial resolution being the result, *e.g.*, Bailey and Hass (1941) converted (±)-pentan-2-ol into its diastereoisomers with L(+)-lactic acid, and then partially separated them by fractional distillation.

(vi) **Selective adsorption.** Optically active substances may be selectively adsorbed by some optically active adsorbent, *e.g.*, Henderson and Rule (1939) partially resolved *p*-phenylenebisiminocamphor on lactose as adsorbent; Bradley and Easty (1951) have found that wool and casein selectively adsorb (+)-mandelic acid from an aqueous solution of (±)-man-

delic acid. A particularly important case of resolution by chromatography is that of Tröger's base (see §2c. VI).

Jamison and Turner (1942) have carried out a chromatographic separation without using an optically active adsorbent; they partially resolved the diastereoisomers of (−)-menthyl (±)-mandelate by preferential adsorption on alumina. It is also interesting to note that the resolution of a racemic acid by salt formation with an optically active base is made more effective by the application of chromatography.

Resolution has also been carried out by vapour-phase chromatography, *e.g.*, *s*-butanol and *s*-butyl bromide have been separated into two overlapping fractions using a column of starch or ethyl tartrate as the stationary phase (Karagounis *et al.*, 1959). Casanova *et al.* (1961) have resolved (±)-camphor by gas chromatography.

Beckett *et al.* (1957) have introduced a novel method for correlating and determining configurations (*cf.* §9). These authors have prepared " stereoselective adsorbents ". These are adsorbents prepared in the presence of a suitable reference compound of known configuration, *e.g.*, silica gel in the presence of quinine. Such an adsorbent exhibits higher adsorptive power for isomers related to the reference compound than for their stereoisomers, provided that their structures are not too dissimilar from that of the reference compound. Thus silica gel prepared in the presence of quinine adsorbs quinine more readily than its stereoisomer quinidine; cinchonidine (configurationally related to quinine) is adsorbed more readily than its stereoisomer cinchonine (configurationally related to quinidine).

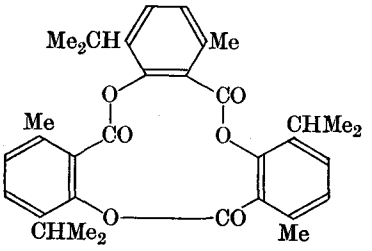
(vii) **Kinetic method of resolution.** Marckwald and McKenzie (1899) found that (−)-menthol reacts more slowly with (−)-mandelic acid than with the (+)-acid. Hence, if insufficient (−)-menthol is used to completely esterify (±)-mandelic acid, the resulting mixture of diastereoisomers will contain more (−)-menthyl (+)-mandelate than (−)-menthyl (−)-mandelate. Consequently there will be more (−)-mandelic acid than (+)-mandelic acid in the ***unchanged*** acid, *i.e.*, a partial resolution of (±)-mandelic acid has been effected (see also §5b. VI).

(viii) Ferreira (1953) has partially resolved (±)-narcotine and (±)-laudanosine (1–2·5 per cent. resolution) ***without*** the use of optically active reagents. He dissolved the racemic alkaloid in hydrochloric acid and then *slowly* added pyridine; the alkaloid was precipitated, and it was found to be optically active. The explanation offered for this partial resolution is as follows (Ferreira). When a crystalline racemic substance is precipitated from solution, a crystallisation nucleus is first developed. Since this nucleus contains a relatively small number of molecules, there is more than an even chance that it will contain an excess of one enantiomorph or other. If it be assumed that the forces acting on the growth of crystals are the same kind as those responsible for adsorption [*cf.* (vi)], the nucleus will grow preferentially, collecting one enantiomorph rather than the other. Crystallisation, when carried out in the usual manner, results in the formation of crystals containing more or less equivalent numbers of both enantiomorphs.

Channel complex formation has also been used to resolve racemic modifications (see Vol. I). This also offers a means of carrying out a resolution without asymmetric reagents, *e.g.*, Schlenk (1952) added (±)-2-chloro-octane to a solution of urea and obtained, on fractional crystallisation, the two urea inclusion complexes urea/(+)-2-chloro-octane and urea/(−)-2-chloro-octane.

Baker *et al.* (1952) have prepared tri-*o*-thymotide, and found that it formed clathrates with ethanol, *n*-hexane, etc. Powell *et al.* (1952) have shown that tri-*o*-thymotide crystallises as a racemate, but that resolution takes place when it forms clathrates with *n*-hexane, benzene or chloroform. By means of seeding and slow growth of a single crystal, it is possible to obtain the

(+)- or (−)-form depending on the nature of the seed. Furthermore, crystallisation of tri-*o*-thymotide (*dl*) from a solvent which is itself a racemic modification (*d'l'*) and which forms a clathrate, produces crystals of the



tri-*o*-thymotide

types *dd'* and *ll'*. Thus such (solvent) racemic modifications can be resolved, *e.g.*, *sec.*-butyl bromide has been resolved in this way.

§**11. The cause of optical activity.** Two important points that arise from the property of optical activity are: What types of structure give rise to optical activity, and why? Fresnel (1822) suggested the following explanation for optical activity in *crystalline* substances such as quartz, basing it on the principle that any simple harmonic motion along a straight line may be considered as the resultant of two opposite circular motions. Fresnel assumed that plane-polarised light, on entering a substance in a direction parallel to its optic axis, is resolved into two beams of circularly polarised light, one right-handed (dextro-) and the other left-handed (lævo-), and both having the same frequency. If these two component beams travel through the medium with the same velocity, then the issuing resultant beam suffers no rotation of its plane of polarisation (Fig. 20 *a*). If the velocity of the lævocircularly polarised component is, for some reason, retarded, then the resultant beam is rotated through some angle to the right (in the direction of the faster circular component; Fig. 20 *b*). Similarly, the resultant beam is rotated to the left if the dextrocircularly polarised component is retarded (Fig. 20 *c*). Fresnel tested this theory by passing

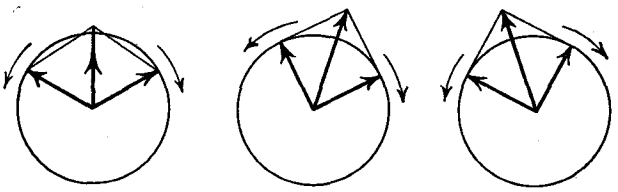


FIG. 2.20.

a beam of plane-polarised light through a series of prisms composed alternately of dextro- and lævorotatory quartz (Fig. 21). Two separate beams emerged, each circularly polarised in opposite senses; this is an agreement with Fresnel's explanation. Fresnel suggested that when plane-polarised light passed through an optically active crystalline substance, the plane of polarisation was rotated because of the retardation of one of the circular components. Stated in another way, Fresnel's theory requires that the refractive indices for dextro- and lævocircularly polarised light should be different for optically active substances. It has been shown mathematically that only a very small difference between these refractive indices gives rise

to fairly large rotations, and that if the refractive index for the lævocircularly polarised light is greater than that for the dextro component, the substance will be dextrorotatory. The difficulty of Fresnel's theory is that it does not explain *why* the two circular components should travel with different velocities. It is interesting to note, however, that Fresnel (1824) suggested that the optical activity of quartz is due to the structure being built up in right- and left-handed spirals (*cf.* §2).

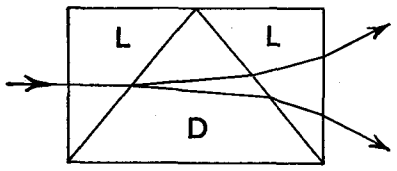


FIG. 2.21.

Now let us consider the problem of optical activity of substances *in solution*. In this case the optical activity is due to the *molecules* themselves, and not to crystalline structure (see also §2). Any *crystal* which has a plane of symmetry *but not a centre of symmetry* (§6) rotates the plane of polarisation, the rotation varying with the direction in which the light travels through the crystal. No rotation occurs if the direction of the light is perpendicular or parallel to the plane of symmetry. If we assume that molecules in a solution (or in a pure liquid) behave as individual crystals, then any molecule having a plane but not a centre of symmetry will also rotate the plane of polarisation, provided that the light travels through the molecule in any direction other than perpendicular (or parallel) to the plane of symmetry. Let us consider the molecule Ca_2bd (Fig. 22). This has a plane of symmetry, and so molecule I and its mirror image II are superimposable. Now let us suppose that the direction of plane-polarised

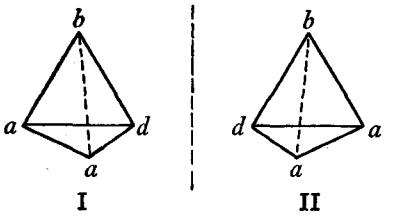


FIG. 2.22.

light passing through molecule I makes an angle $\theta°$ with the plane of symmetry, and that the resultant rotation is $+\alpha°$. Then if the direction of the light through molecule II also makes an angle $\theta°$ with the plane of symmetry, the resultant rotation will be $-\alpha°$. Thus the *total* rotation produced by molecules I and II is *zero*. In a solution of compound Ca_2bd, there will be an *infinite number of molecules in random orientation*. Statistically one can expect to find that whatever the angle θ is for molecule I, there will always be molecule II also being traversed by light entering at angle θ. **Thus, although each individual molecule rotates the plane of polarisation by an amount depending on the value of θ, the statistical sum of the contributions of the individual molecules will be zero.**

When a molecule is not superimposable on its mirror image, then if only one enantiomorph is present in the solution, the rotation produced by each individual molecule will (presumably) depend on the angle of incidence (with respect to any face), but there will be no compensating molecules (*i.e.*, mirror image molecules) present. Hence, in this case, there will be a net

rotation that is *not* zero, the actual value being the statistical sum of the individual contributions (which are all in the *same* direction). Thus, if we consider the behaviour of a compound in a solution (or as a pure liquid) *as a whole*, then the observed experimental results are always in accord with the statement that **if the molecular structure of the compound is asymmetric, that compound will be optically active** (§2). Any compound composed of molecules possessing a plane but not a centre of symmetry is, considered *as a whole*, optically inactive, the net zero rotation being the result of " external compensation " (*cf.* §7a). This point is of great interest in connection with flexible molecules (§4). Let us consider *meso*tartaric acid, a compound that is optically inactive by internal compensation (§7b). X-ray studies (Stern *et al.*, 1950) have shown that the staggered form of the molecule is the favoured one (Fig. 23 *a*). This has a centre of symmetry, and so molecules in this configuration are *individually*

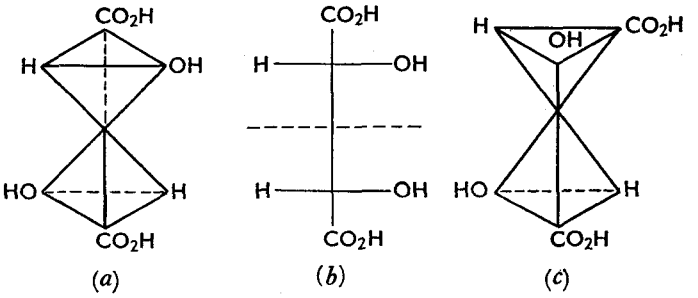


FIG. 2.23.

optically inactive. On the other hand, *meso*tartaric acid is usually represented by the plane-diagram formula in Fig. 23 (*b*). This corresponds to the eclipsed form, and has a plane of symmetry. In this conformation the *individual* molecules are optically active except when the direction of the light is perpendicular (or parallel) to the plane of symmetry; the net rotation is zero by " external compensation ". It is possible, however, for the molecule to assume, at least theoretically, many conformations which have no elements of symmetry, *e.g.*, Fig. 23 (*c*). All molecules in this conformation will contribute *in the same direction* to the net rotation. If the *total number* of molecules present were in this conformation, then *meso*tartaric acid would have some definite rotation. On the theory of probability, however, for every molecule taking up the conformation in Fig. 23 (*c*), there will also be present its mirror image molecule, thereby giving a net *zero* rotation due to " external compensation ". As we have seen, *meso*tartaric acid is optically inactive (as shown experimentally), and by common usage the inactivity is said to be due to *internal compensation* (§7b).

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CHAPTER III

NUCLEOPHILIC SUBSTITUTION AT A SATURATED CARBON ATOM

§1. The most extensively studied type of heterolytic substitution in saturated compounds is the nucleophilic type, *i.e.*, the S_N1 and S_N2 mechanisms.

One-stage process. When two molecules simultaneously undergo covalency change in the rate-determining step, the mechanism is called ***bimolecular*** and is labelled S_N2 (substitution, nucleophilic, bimolecular).

Two-stage process. In this case the first step is the *slow* heterolysis of the compound to form a carbonium ion, and this is then followed by the second step of ***rapid*** combination of the carbonium ion with the nucleophilic reagent. The rate-determining step is the first, and since in this step only *one* molecule is undergoing covalency change, the mechanism is called ***unimolecular*** and is labelled S_N1 (substitution, nucleophilic, unimolecular).

The symbols S_N1 and S_N2 were introduced by Ingold (1928), the number in the symbol referring to the *molecularity* of the reaction and *not* to the kinetic order. Any complex reaction may be designated by the molecularity of its rate-determining stage, the molecularity of the rate-determining stage being defined as the *number of molecules* necessarily undergoing covalency change (Ingold, 1933).

The main difference between the two mechanisms is the kinetic order of the reaction. S_N2 reactions would be expected to be second order (first order with respect to each reactant), whereas S_N1 reactions would be expected to be first order. These orders are only true under certain circumstances. In a bimolecular reaction, if both reactants are present in small and controllable concentrations, the reaction will be of the second order. If, however, one of the reactants is in constant excess (*e.g.*, one reactant is the solvent), then the mechanism is still bimolecular but the reaction is now of the first order. Unimolecular mechanisms often lead to first-order kinetics but may, under certain circumstances, follow a complicated kinetic expression. Since, however, it is possible to derive such an equation theoretically, it may be still decided whether the mechanism is S_N1 by ascertaining whether the data fit this kinetic expression.

Another important difference between the S_N2 and the S_N1 mechanism is that in the former the configuration of the molecule is *always* inverted, whereas in the latter there may be inversion and/or retention, the amount of each depending on various factors (see later).

The nucleophilic reagent may be negatively charged or neutral; the primary requirement is that it must possess an unshared pair of electrons which it can donate to a nucleus capable of sharing this pair. One widely studied example of nucleophilic aliphatic substitution is that of the hydrolysis of alkyl halides (T.S. = transition state; see also Vol. I):

$$\mathbf{S_N2}\quad Y^- + R{-}X \xrightarrow{\text{slow}} \underset{\text{T.S.}}{Y^{\delta-}\cdots R\cdots X^{\delta-}} \xrightarrow{\text{fast}} Y{-}R + X^-$$

$$\mathbf{S_N1}\quad R{-}X \xrightarrow{\text{slow}} \underset{\text{T.S.}}{R^{\delta+}\cdots X^{\delta-}} \xrightarrow{\text{fast}} R^+ + X^-$$

$$R^+ + Y^- \xrightarrow{\text{fast}} RY$$

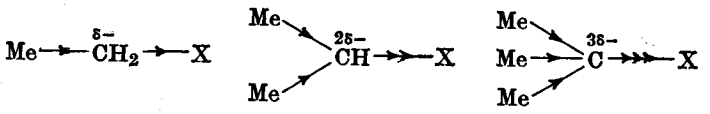
Of particular interest is the evidence for the S_N1 mechanism. A fundamental part of this mechanism is the postulate of carbonium ions as transient intermediates; but there appears to be no direct physical evidence for the presence of *aliphatic* carbonium ions. Symons *et al.* (1959) have shown that monoaryl-

carbonium ions are stable in dilute solutions of sulphuric acid. They have also found that the spectroscopic examination of solutions of *t*-butanol and *iso*butene in sulphuric acid shows a single measurable ultraviolet band in both solutions. This band appears slowly according to the first-order rate law for *t*-butanol, but very rapidly for the olefin; the solutions are stable (and reproducible). The authors conclude that there are trimethylcarbonium ions, CMe_3^+, in solution, and that it is probable that this ion is planar. Symons *et al.* (1961) have also obtained evidence, from ultraviolet studies, for the existence of the allyl carbonium ion in sulphuric acid; they examined solutions of allyl alcohol, chloride, bromide, etc., in sulphuric acid.

On the other hand, triarylcarbonium ions have been obtained as salts, *e.g.*, triphenylmethyl perchlorate, $Ph_3C^+ClO_4^-$, and fluoroborate, $Ph_3C^+BF_4^-$ (Dauben jun. *et al.*, 1960).

§2. Any factor that affects the energy of activation (E) of a given type of reaction will affect the rate and/or the mechanism. Attempts have been made to calculate E in terms of bond strengths, the steric factor, heats of solutions of ions, etc., but apparently the results are conflicting. The following discussion is therefore largely qualitative, and because of this, one cannot be sure which are the predominant factors in deciding the energy of activation. We shall discuss, for the hydrolysis of alkyl halides, the influence of the following factors: The nature of R (polar and steric effects); the nature of X and Y; and the nature of the solvent.

§2a. The nature of R. (*a*) *Polar effects.* Let us consider the series EtX, *i*-PrX, and *t*-BuX. Since the methyl group as a +I effect, the larger the number of methyl groups on the carbon atom of the C—X group, the greater will be the electron density on this carbon atom. This may be represented qualitatively as follows:



This increasing negative charge on the central carbon atom increasingly opposes attack at this carbon by a negatively charged nucleophilic reagent; it also opposes, to a lesser extent, attack by a neutral nucleophilic reagent since this still donates an electron pair. Thus the formation of the transition state for the S_N2 mechanism is opposed more and more as the charge on the central carbon atom increases. (There is also an increasing steric effect operating; this is dealt with in §2b.) The anticipated result, therefore, is that as the number of methyl groups increases on the central carbon atom, the S_N2 mechanism is made more difficult in passing from EtX to *t*-BuX. On the other hand, since the S_N1 mechanism involves ionisation of RX (in the rate-determining step), any factor that makes easier the ionisation of the molecule will therefore facilitate the S_N1 mechanism. The anticipated result, therefore, is that the greater the negative charge on the central carbon atom, the easier will be the ionisation of RX since X is displaced with its covalent electron pair; thus the tendency for the S_N1 mechanism should increase from EtX to *t*-BuX.

These predicted results have been verified experimentally. Hughes, Ingold *et al.* (1935–1940) examined the rates of hydrolysis of alkyl bromides in alkaline aqueous ethanol at 55°:

	MeBr	EtBr	*i*-PrBr	*t*-BuBr
2nd-order rate const. × 10^5	2140	170	4·7	
1st-order rate const. × 10^5			0·24	1010

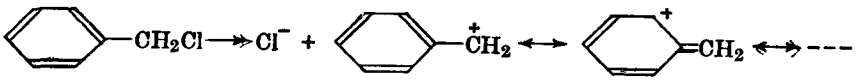
It can be seen from these results that MeBr and EtBr undergo hydrolysis by the S_N2 mechanism, *i*-PrBr by *both* S_N2 and S_N1, and *t*-BuBr by S_N1 only. Thus, as the polar effects in the alkyl group produce an increasing electron density on the central carbon atom, the rate of the S_N2 mechanism decreases and a point is reached where the mechanism changes over to S_N1. With *i*-PrBr both S_N2 and S_N1 mechanisms operate, and the rate of the S_N2 mechanism is much less than that of the S_N2 mechanism for EtBr. With *t*-BuBr the electron density on the central carbon atom is so great that the S_N2 mechanism is completely inhibited; a very rapid hydrolysis occurs by the S_N1 mechanism only. Since the mechanism is S_N1, it therefore means that the hydroxide ion does not enter into the rate-determining step of the hydrolysis (§1). This has been proved as follows. The hydrolysis of *t*-BuBr was carried out in an alkaline solution containing less than the equivalent amount of hydroxide ion (compared with the alkyl bromide). Thus, although the solution was originally alkaline, as the hydrolysis proceeds, the solution becomes neutral and finally acid; nevertheless, the rate constant of the hydrolysis remained unchanged.

As pointed out above, there are reactions which occur under intermediate conditions, *i.e.*, at the border-line between the extreme S_N1 and S_N2 mechanisms. Some authors believe that in this border-line region there is only *one* mechanism operating, *e.g.*, Prevost (1958) has postulated, on theoretical grounds, the existence of a more universal " mesomechanism ". There is, however, much experimental work in favour of concurrent S_N1 and S_N2 mechanisms operating. Gold (1956) has described evidence for this view, and more recently Swart *et al.* (1961) have shown that the exchange reaction between diphenylmethyl chloride and radiochlorine (as LiCl*) in dimethylformamide occurs by a simultaneous S_N1–S_N2 mechanism.

The actual position where the mechanism changes over from S_N2 to S_N1 in a graded series, *e.g.*, in the one already described, is not fixed but depends on other factors such as the concentration and nature of the nucleophilic reagent, and on the nature of the solvent (see below).

Experimental work has shown that higher *n*-alkyl groups behave similarly to ethyl. For a given set of conditions, the kinetic order is the same, but the rates tend to decrease as the number of carbon atoms increases, *e.g.*, Hughes, Ingold *et al.* (1946, 1948) showed that the reactions between primary alkyl bromides and ethoxide ion in dry ethanol are all S_N2, and their relative rates (at 55°) are Me, 17·6; Et, 1·00; *n*-Pr, 0·31; *n*-Bu, 0·23; *n*-pentyl, 0·21. Similar results were obtained for secondary alkyl groups. In these cases the mechanisms were both S_N2 and S_N1, but the rates for one or other order were reasonably close, *e.g.*, for the second-order reactions of secondary bromides with ethoxide ion in dry ethanol at 25°, Hughes, Ingold *et al.* (1936–) found that the relative rates were: *i*-Pr, 1·00; 2-*n*-Bu, 1·29; 2-*n*-pentyl, 1·16; 3-*n*-pentyl, 0·93. These authors also showed that higher tertiary alkyl groups behaved similarly to *t*-Bu, all showing a strong tendency to react by the S_N1 mechanism.

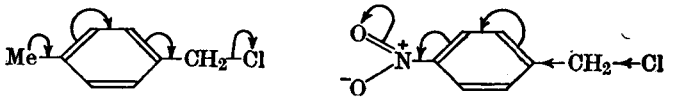
When hydrogen atoms in methyl chloride are replaced by phenyl groups, the mechanism of the hydrolysis may be changed (from S_N2). The presence of a phenyl group produces a carbonium ion which can be stabilised by resonance; this acts as the driving force to produce ionisation; *e.g.*,



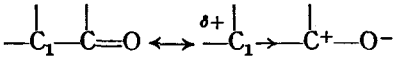
Thus one can anticipate that as the number of phenyl groups increases, the stability of the carbonium ion produced will increase, *i.e.*, the carbonium ion will be formed more readily and consequently the S_N1 mechanism will

be increasingly favoured. Thus in the series MeCl, $PhCH_2Cl$, Ph_2CHCl, Ph_3CCl, it has been found that in alkaline solution the hydrolysis of methyl chloride proceeds by the S_N2 mechanism, that of phenylmethyl chloride by both S_N2 and S_N1, and that of diphenylmethyl chloride by S_N1; the hydrolysis of triphenylmethyl chloride is too fast to be measured, but this high rate is very strong evidence for an S_N1 mechanism.

Various groups in the *para*-position of the phenyl nucleus either assist or oppose ionisation. It has been found that alkyl groups enhance ionisation in the order Me > Et > *i*-Pr > *t*-Bu. Since this order is the reverse of that expected from the general inductive effects of these groups, it has been explained by the hyperconjugative effects of these groups (which are in this order; see Vol. I). On the other hand, a nitro-group retards the ionisation, and this attributed to the electron-withdrawing effect of this group.

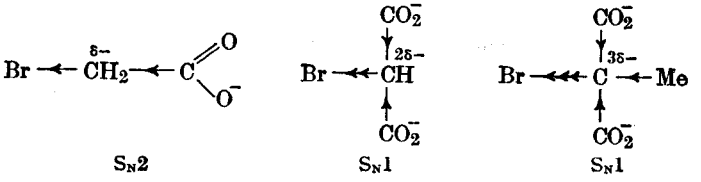


Another group of interest is the carbonyl group; this is electron-attracting (through resonance):



Thus the covalent electron-pair of a halogen atom attached to C_1 is drawn closer to C_1 and consequently it is more difficult for this halogen atom to ionise. Thus the S_N1 mechanism is opposed, and at the same time, the small positive charge on C_1 encourages the S_N2 mechanism. It can therefore be anticipated that any electron-attracting (or withdrawing) group will tend to inhibit the S_N1 mechanism for a compound with an α-halogen atom. Such groups are CO_2R, NO_2, CN, etc.; *e.g.*, both ethyl α-bromopropionate and diethyl bromomalonate undergo hydrolysis by the S_N2 mechanism.

On the other hand, the carboxylate ion has a +I effect due to its negative charge and hence its presence should enhance the ionisation of an α-halogen atom. At the same time, the α-carbon atom tends to acquire a small negative charge, and this will tend to oppose the approach of a hydroxide ion. Thus there are two influences acting, one increasing the tendency for the S_N1 mechanism and the other decreasing the tendency for the S_N2; both therefore oppose the S_N2 mechanism. Some experimental results that illustrate these arguments are the alkaline hydrolyses of the following compounds:



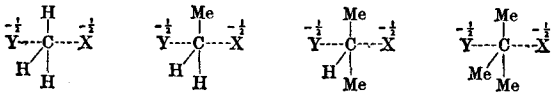
S_N2 S_N1 S_N1

§2b. The nature of R. (*b*) *Steric effects.* In the transition state for the S_N2 mechanism, there are five atoms or groups bonded or partly bonded to the reaction carbon atom (see §4). Thus the larger the bulk of these groups, the greater will be the compression energy (*i.e.*, greater steric strain) in the transition state and consequently the reaction will be *sterically hindered.* The problem is different for the S_N1 mechanism. Here, the transition state does not contain more than four groups attached to the reaction carbon atom and hence one would expect that steric hindrance should be less important. On the other hand, if the molecule undergoing

the S_N1 mechanism contains particularly large groups, then the first step of ionisation may relieve the steric strain (§4a. II) and so assist the formation of the carbonium ion, *i.e.*, the reaction may be *sterically accelerated.*

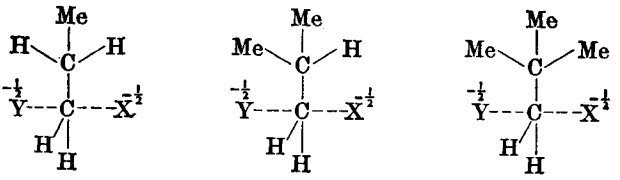
Let us now examine some examples involving steric effects.

(i) The following series of alkyl halides, MeX, EtX, *i*-PrX and *t*-BuX, may be made to undergo the S_N2 mechanism under suitable conditions (*cf.* §2a); the transition state contains three σ-bonds (sp^2 hybridisation) in one plane and two partial bonds which are collinear and perpendicular to this plane. Thus we have:



Inspection of these transition states shows that steric hindrance increases as the hydrogen atoms are progressively replaced by methyl groups. This increasing steric effect has been demonstrated by Hughes *et al.* (1946), who showed that the relative reactivities of the alkyl bromides towards iodide ions in acetone (by the S_N2 mechanism) are: Me, 10,000; Et, 65; *i*-Pr, 0·50; *t*-Bu, 0·039.

Now let us consider *n*-propyl, *iso*butyl and *neo*pentyl halides; their transition states will be (for the S_N2 mechanism):



At first sight one would not expect *n*-PrX to show an added steric effect when compared with EtX since the added methyl group can occupy a position close to the plane of the transition state (*i.e.*, the plane containing the three σ-bonds), and so would not offer any appreciable steric hindrance. In practice, however, *n*-propyl halides are less reactive than the corresponding ethyl halides (*cf.* §2a). The reason for this relatively large decreased reactivity is not certain. Magat *et al.* (1950) have offered the following explanation. The smaller the number of conformations available in the activated as compared with the initial state produces a decrease in the frequency factor (A in the Arrhenius equation $k = Ae^{-E/RT}$). In *n*-propyl halides (2 H and 1 Me) there is only one conformation for the transition state whereas for ethyl halides (3 H) there are three equivalent conformations. Thus the frequency factor for *n*-propyl halides is 1/3 that for the ethyl halides, and so the reaction rate (k) of the former will be 1/3 that of the latter (on the assumption that E of both reactions is the same).

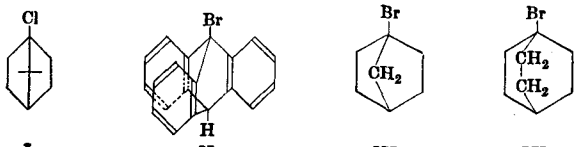
In *iso*butyl halides the methyl groups will produce a large steric effect since at least one methyl group will be fairly close to X or Y. It has been shown experimentally that *iso*butyl halides are less reactive than *n*-propyl halides. Finally, in *neo*pentyl halides, the presence of three methyl groups produces a very large steric effect. In the " normal " transition state, the entering and displaced groups are collinear. This is readily possible with all the halides except possibly *iso*butyl halides; but it is not possible with *neo*pentyl halides because of the presence of the three methyl groups (in the *t*-butyl group). Thus in the transition state involving the *neo*pentyl radical, the Y---C---X bonds are believed not to be collinear but " bent away " from the *t*-butyl group. Such a " bent " transition state has a large compression energy and so is far more difficult to form than a " normal "

transition state. Experimental data are in agreement with these ideas, *e.g.*, Hughes *et al.* (1946) showed the following relative (S_N2) reaction rates towards the ethoxide ion at 95°:

$$Et : i\text{-}Bu : Me_3C{\cdot}CH_2 :: 1 : 0{\cdot}04 : 10^{-5}$$

These very slow S_N2 reactions of *neo*pentyl halides occur with the *neo*pentyl radical remaining intact. By changing the solvent conditions so that the mechanism becomes S_N1, the products are no longer *neo*pentyl derivatives but rearranged products formed by a 1,2-shift (see §23d. VIII).

(ii) A very interesting example of steric hindrance is the case of 1-chloroapocamphane (I). Bartlett *et al.* (1938) found that this compound does not react with reagents that normally react with alkyl halides, *e.g.*, it is unaffected when refluxed with aqueous ethanolic potassium hydroxide or



I II III IV

with ethanolic silver nitrate. As we have seen, the hydrolysis of *t*-butyl chloride takes place by the S_N1 mechanism. 1-Chloroapocamphane is a tertiary chloride, but since it does not ionise, the S_N1 mechanism is not possible. This failure to ionise is believed to be due to the fact that the carbonium ion is flat (sp^2 hybridisation). Removal of the chloride ion from (I) would produce a positive carbon atom which *cannot* become planar because of the steric requirements of the bridged-ring structure. Furthermore, since the rear of the carbon atom of the C—Cl group is " protected " by the bridge, the S_N2 mechanism is not possible (since the nucleophilic reagent must attack from the rear; see §4). The failure to replace bromine in 1-bromotriptycene (II) is explained similarly (Bartlett *et al.*, 1939). On the other hand, Doering *et al.* (1953) showed that (III) gave the corresponding alcohol when heated with aqueous silver nitrate at 150° for two days, and (IV) gave the corresponding alcohol after four hours at room temperature. The reason for this behaviour (as compared with the other bridged compounds) is not certain, but it has been suggested that the extra bonds in the larger bridge in (IV) help to relieve the strain in the formation of the carbonium ion which tries to assume a planar configuration.

(iii) Brown *et al.* (1949) showed that the solvolysis of tertiary halides is subject to steric acceleration. (*Solvolysis* is the nucleophilic reaction in which the *solvent* is the nucleophilic reagent.)

$$R_3C{-}X \xrightarrow{H_2O} R_3C^+ + X^-$$

tetrahedral (large strain) — planar; trigonal (small strain)

It was shown that as R increases in size, the rate of solvolysis increases. However, the larger R is, the more slowly will the carbonium ion be expected to react with the solvent molecules, and so a factor is introduced which opposes steric acceleration. Carbonium ions can undergo elimination reactions to form olefins (see also Vol. I), and Brown *et al.* (1950) have shown that this elimination reaction increases as the R groups become larger.

§2c. The nature of the halogen atom. Experimental work has shown that the nature of the halogen atom has very little effect, if any, on *mechanism*, but it does affect the *rate* of reaction for a given mechanism; *e.g.*, it has been found that in S_N1 reactions, the rate follows the order

RI > RBr > RCl. It has been suggested that a contributing factor to this order is steric strain, since the volume order of these halogen atoms is I > Br > Cl. Another contributing factor is the increase in energy of activation in the order RCl > RBr > RI, since the bond to be broken increases in strength in this order; the bond energies are: C—Cl, 77 kg.cal.; C—Br, 65 kg.cal.; C—I, 57 kg.cal. These energy differences also explain the order of reactivity RI > RBr > RCl in S_N2 reactions.

§2d. The nature of the nucleophilic reagent. The more pronounced the nucleophilic activity of the reagent, *i.e.*, the greater its electron availability, the more the S_N2 mechanism will be favoured as compared with the S_N1 mechanism, since in the latter the nucleophilic reagent does not enter into the rate-determining step.

It can be anticipated that as nucleophilic activity decreases, the rate of an S_N2 reaction will decrease for a given series of substitutions (under similar conditions), and when the nucleophilic activity is sufficiently low, the mechanism may change from S_N2 to S_N1. Hughes, Ingold *et al.* (1935) examined the rates of decomposition of various trimethylsulphonium salts in ethanol ($Me_3S^+X^- \longrightarrow Me_2S + MeX$) and obtained the following results (see also §4):

Anion	OH^-	OPh^-	HCO_3^-	Br^-	Cl^-
2nd-order rate const. × 10^5	74,300	1340	—	—	—
1st-order rate const. × 10^5	—	—	7·38	7·85	7·32

It can be seen from these results that the strong nucleophiles OH^- and OPh^- react rapidly by the S_N2 mechanism and the other, and weaker, nucleophiles react at about the same slow speed by the S_N1 mechanism.

Although many kinetic investigations of displacement reactions with alkyl halides have been carried out, relatively little information is available for determining nucleophilicity. One set of data that may be cited is that obtained from the reaction between methyl iodide and various bases in benzene at 25° (Hinshelwood *et al.*, 1935):

	Pyridine	Me_3N	Et_3N	Quinoline
Relative rate	1	1730	144	0·26

A point of interest in connection with the nature of the nucleophile is that when it affects the rate of substitution, the reaction is usually proceeding by the S_N2 mechanism. When the nature of the nucleophile has very little effect on the rate, then the reaction is probably S_N1. Another point to note is that steric effects in the nucleophile will also affect the rate of reaction, and this is probably a contributing factor to the different rates observed with reagents with similar nucleophilicity.

In general, it has been found that within a given periodic group, the nucleophilic activity increases with the atomic number of the atom, *e.g.*,

$$I^- > Br^- > Cl^- > F^-; \quad RS^- > RO^-.$$

This order is opposite to that anticipated on the basis of basicities (and steric effects) of the different nucleophiles. This lack of some sort of parallelism between nucleophilic reactivity and basicity is unexpected, since both of these properties depend on the donating power of the donor atom. However, as a result of experimental work, it is now well established that

nucleophilic reactivity does not follow the order of increasing basicity towards protons, but varies with the nature of the reaction and with the reaction conditions.

§2e. The effect of the solvent on mechanisms and reaction rates. Experimentally, it has been found that the ionising power of a solvent depends on at least two factors, dielectric constant and solvation.

Dielectric constant. A very rough generalisation is that ionisation of the solute increases both in amount and speed the higher the dielectric constant of the solvent.

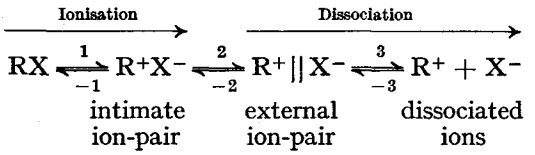
Solvation. This factor appears to be more important than the dielectric constant. Solvation is the interaction between solvent molecules and solute molecules, and is partly accounted for by the attraction of a charge for a dipole. If the solute has polarity, then solvent molecules will be attracted to the solute molecules. The greater the polarity of the solvent, the greater the attraction and consequently the more closely the solvent molecules will be drawn to the solute molecules. Thus more electrostatic work is done and so more energy is lost by the system, which therefore becomes more stable. Thus increasing the dielectric constant of the solvent increases the ionising potentiality of the solute molecules, and the higher the polarity of the solvent the more stable becomes the system due to increased solvation. Solvation, however, may also be partly due to certain chemical properties, *e.g.*, sulphur dioxide has an electrophilic centre (the sulphur atom carries a positive charge); hydroxylic solvents can form hydrogen bonds.

There is also another problem that may arise. This is that although the solute molecules have ionised, the oppositely charged pair are enclosed in a " cage " of surrounding solvent molecules and may therefore recombine before they can escape from the cage. Such a complex is known as an *ion-pair*, and their recombination is known as *internal return*. It has now been shown that many organic reactions proceed *via* ion-pairs rather than dissociated ions. According to some authors there are two types of ion-pairs:

(i) *Intimate* or *internal* ion-pairs. These are enclosed in a solvent cage and the ions of the pair are *not* separated by solvent molecules.

(ii) *Loose* or *external* ion-pairs. The ions of these pairs are separated by solvent molecules but still behave as a pair. External ion-pairs may also give rise to ion-pair return (*external return*), but they are more susceptible to attack by other reagents than are intimate ion-pairs. Many workers believe it unnecessary to postulate the existence of this type of ion-pair.

Thus, when ionisation takes place, the following steps are possible:



N.B. (i) −1 is internal return, and it appears uncertain whether this type of ion-pair is a transition state or an intermediate; (ii) −2 is external return; (iii) only equilibrium 3 is sensitive to a common ion effect; this is because an ion-pair behaves as a single particle, as has been shown by the effect on the depression of the freezing point ($i = 1$).

A number of equations have been proposed correlating rates and the nature of the solvent, but none is completely general. Hughes and Ingold (1935, 1948) proposed the following qualitative theory of solvent effects: (i) Ions and polar molecules, when dissolved in polar solvents, tend to become solvated. (ii) For a given solvent, solvation tends to increase with

increasing magnitude of charge on the solute molecules or ions. (iii) For a given solute, solvation tends to increase with the increasing dipole moment of the solvent. (iv) For a given magnitude of charge, solvation decreases as the charge is spread over a larger volume. (v) The decrease in solvation due to the dispersal of charge will be less than that due to its destruction.

Since the rate-determining step in the S_N1 mechanism is ionisation, any factor assisting this ionisation will therefore facilitate S_N1 reactions. Solvents with high dipole moments are usually good ionising media and, in general, it has been found that the more polar the solvent the greater is the rate of S_N1 reactions. We have, however, also to consider the problem of solvation.

$$R{-}X \xrightarrow{\text{slow}} \overset{\delta+}{R}\cdots\overset{\delta-}{X} \xrightarrow{\text{fast}} R^+ + X^- \xrightarrow[\text{fast}]{OH^-} ROH$$

Increasing the polarity of the solvent will greatly increase the reaction rate, and since the transition state has a larger charge than the initial reactant molecule, the former is more solvated than the latter (rule ii). Thus the transition state is more stabilised than the reactant molecule. Thus solvation lowers the energy of activation and so the reaction is assisted.

The rates of S_N2 reactions are also affected by the polarity of the solvent.

$$HO^{\curvearrowright} R\text{—}X^{\curvearrowright} \xrightarrow{\text{slow}} \overset{\delta-}{HO}\cdots R\cdots\overset{\delta-}{X} \xrightarrow{\text{fast}} HO{-}R + X^-$$

A solvent with high dipole moment will solvate both the reactant ion and the transition state, but more so the former than the latter, since in the latter the charge, although unchanged in magnitude ($\delta- = -1/2$), is more dispersed than in the former (rule iv). Thus solvation tends to stabilise the reactants more than the transition state, *i.e.*, the activation energy is increased and so the reaction is retarded.

Now let us consider the Menschutkin reaction:

$$R_3\ddot{N}^{\curvearrowright} R\text{—}X^{\curvearrowright} \longrightarrow R_3\overset{\delta+}{N}\cdots R\cdots\overset{\delta-}{X} \longrightarrow R_4N^+X^-$$

The charge on the transition state is greater than that on the reactant molecules; hence the former is more solvated than the latter. Thus the energy of activation is lowered and the rate of reaction thereby increased. Also, the greater the polarity of the solvent, the greater should be the solvation. The foregoing predictions have been observed experimentally.

In the following S_N2 reaction, charges decrease in the transition state,

$$HO^{\curvearrowright} R\overset{+}{N}R_3 \longrightarrow \overset{\delta-}{HO}\cdots R\cdots\overset{\delta+}{N}R_3 \longrightarrow HOR + R_3N$$

and hence increasing the polarity of the solvent will retard the reaction; and retardation will be greater than that in the S_N2 hydrolysis of alkyl halides (see above; only the hydroxide ion is charged in this case).

The polarity of the solvent not only affects rates of reactions, but may also change the mechanism of a reaction, *e.g.*, Olivier (1934) showed that the alkaline hydrolysis of benzyl chloride in 50 per cent. aqueous acetone proceeds by both the S_N2 and S_N1 mechanisms. In water as solvent, the mechanism was changed to mainly S_N1. The dipole moment of water is greater than that of aqueous acetone, and consequently the ionisation of benzyl chloride is facilitated.

Another example we shall consider is the hydrolysis of the alkyl bromides, MeBr, EtBr, *i*-PrBr and *t*-BuBr. As we have seen (§2a), Hughes, Ingold *et al.* showed that in aqueous alkaline ethanol the mechanism changed from S_N2 for MeBr and EtBr to both S_N2 and S_N1 for *i*-PrBr, and to S_N1

for *t*-BuBr. These results were explained by the +I effects of the R groups, but it also follows that the greater the ionising power of the solvent, the less will be the +I effect of an R group necessary to change the mechanism from S_N2 to S_N1. Formic acid has been found to be an extremely powerful ionising solvent for alkyl halides, and the relative rates of hydrolysis, at 100°, for the above series of bromides with the very weak nucleophilic reagent water, dissolved in formic acid, was found to be (Hughes *et al.*, 1937, 1940): MeBr, 1·00; EtBr, 1·71; *i*-PrBr, 44·7; *t*-BuBr, *ca.* 10^8. This continuous increase in reaction rate shows that the mechanism is mainly S_N1 (the rate increasing with the increasing +I effect of the R group). Thus both MeBr and EtBr are also hydrolysed by the S_N1 mechanism under these favourable conditions of high solvent-ionising power.

Solvents may also affect the proportions of the products in competitive reactions, *i.e.*, the attack on the same substrate by two substituting reagents in the same solution:

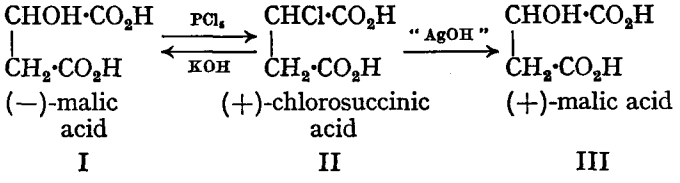
$$RY \xleftarrow{Y} RX \xrightarrow{Z} RZ$$

In the S_N2 mechanism there is only one reaction step, and so the overall rate and product ratio will be determined by that stage. In the S_N1 mechanism, however, the rate is determined by the rate of ionisation of RX, and the product ratio is thus determined by the competition of the fast second steps. It therefore follows that for solvent changes, in the S_N2 mechanism the rate and product ratio will proceed in a parallel fashion, whereas in the S_N1 mechanism the rate and product ratio will be independent of each other. A simple example that illustrates this problem is the solvolysis of benzhydryl chloride (diphenylmethyl chloride). Hammett *et al.* (1937, 1938) showed that the solvolysis of benzhydryl chloride in initially neutral aqueous ethanol gave benzhydryl ethyl ether and benzhydrol. Hughes, Ingold *et al.* (1938) showed that if ethanol is first used as solvent and then water is progressively added, the overall rate increases, but there is very little increase in benzhydrol formation; the main effect is an increased rate of formation of benzhydryl ethyl ether. Thus the rate of the reaction and the ratio of the products are determined independently; this is consistent with the S_N1 mechanism but not with the S_N2.

It can be seen from this example that kinetic solvent effects may be used to differentiate between S_N2 and S_N1 mechanisms.

§3. The Walden inversion (Optical inversion). By a series of replacement reactions, Walden (1893, 1895) transformed an optically active compound into its enantiomorph. In some cases the product is 100 per cent. optically pure, *i.e.*, the inversion is quantitative; in other cases the product is a mixture of the (+)- and (−)-forms in unequal amounts, *i.e.*, inversion and retention (racemisation) have taken place.

The phenomenon was first discovered by Walden with the following reactions:



(−)-malic acid — I

(+)-chlorosuccinic acid — II

(+)-malic acid — III

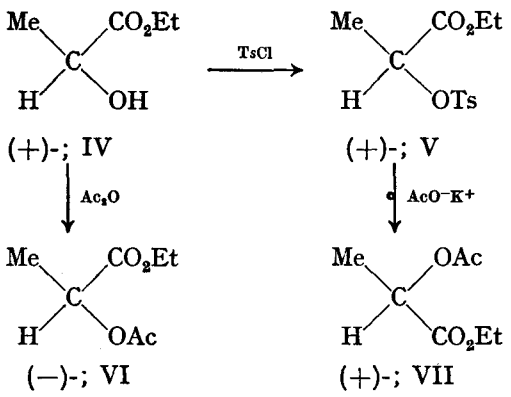
This conversion of the (−)-form into the (+)-form constitutes a Walden inversion. The Walden inversion was " defined " by Fischer (1906) as the conversion of the (+)-form into the (−)-form, or *vice versa*, without recourse to resolution. In one, and only one, of the two reactions, must there be an

interchange of position between the two groups, *e.g.*, if the configuration of (I) corresponds with that of (II), the inversion of configuration must have taken place between (II) and (III). Now that the mechanism of substitution at a saturated carbon has been well worked out, the term *Walden inversion* is applied to any *single* reaction in which inversion of configuration occurs.

As the above experiment stands, there is no way of telling which stage is accompanied by inversion. As we have seen (§5b. II), change in sign of rotation does not necessarily mean that inversion configuration has occurred. Various methods of correlating configuration have already been described (§5a. II), but here we shall describe the method where bonds attached to the asymmetric carbon atom are broken during the course of the reactions. This method was established by Kenyon *et al.* (1925), who carried out a series of reactions on optically active hydroxy compounds. Now it has been established that in the esterification of a monocarboxylic acid by an alcohol under ordinary conditions, the reaction proceeds by the acyl-oxygen fission mechanism (see also Vol. I); thus:

$$R{\cdot}CO\text{—}OH \quad H\text{—}OR' \longrightarrow R{\cdot}CO{\cdot}OR' + H_2O$$

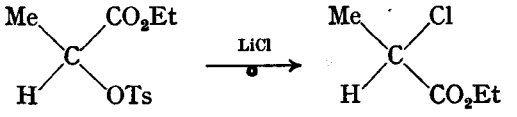
Kenyon assumed that in all reactions of this type the R′—O bond remained intact and consequently no inversion of the alcohol is possible. The following chart shows a series of reactions carried out on ethyl (+)-lactate; Ts = tosyl group = *p*-toluenesulphonyl group, *p*-Me·C_6H_4·SO_2-; the symbol $\xrightarrow{\text{inv.}}$ is used to represent inversion of configuration in that step. (IV) and



(VI) have the same relative configurations even though the sign of rotation has changed. Similarly, (IV) and (V) have the same relative configurations. Reaction of (V) with potassium acetate, however, produces (VII), the enantiomorph of (VI). Therefore inversion must have occurred in the formation of (VII); (V) and (VI) are produced without inversion since in these cases the C—O bond in (IV) is never broken. It should be noted here that if inversion is going to take place at all, the *complete group* attached to the asymmetric carbon atom must be removed (in a displacement reaction) (*cf.* Fischer's work on (+)-*iso*propylmalonamic acid, §3a. II). The converse, however, is not true, *i.e.*, removal of a complete group does not invariably result in inversion (see later, particularly §4).

The above series of reactions has been used as a standard, and all closely analogous reactions are assumed to behave in a similar way, *e.g.*, the action of lithium chloride on the tosylate (V) is assumed to be analogous to that

of potassium acetate, and the chloride produced thus has an inverted configuration:



V

By similar procedures, Kenyon *et al.* (1929, 1930) showed that (+)-octan-2-ol and (+)-2-chloro-, 2-bromo- and 2-iodo-octane have the same relative configurations; and also that (+)-α-hydroxyethylbenzene (Ph·CHOH·Me), (+)-α-chloro- and (+)-α-bromoethylbenzene have the same relative configurations (see also the S_N2 mechanism, §4).

§4. Mechanism of the Walden inversion. As the result of a large amount of work on the Walden inversion, it has been found that at least three factors play a part in deciding whether inversion or retention (racemisation) will occur: (i) the nature of the reagent; (ii) the nature of the substrate; (iii) the nature of the solvent. Hence it is necessary to explain these factors when dealing with the mechanism of the Walden inversion.

Many theories have been proposed, but we shall discuss only the Hughes–Ingold theory, since this is the one now accepted. According to this theory, aliphatic nucleophilic substitution reactions may take place by either the S_N2 or S_N1 mechanism (see also §5).

S_N2 $\quad HO^- + R{-}X \longrightarrow HO^{\delta-}\cdots R\cdots X^{\delta-} \longrightarrow HO{-}R + X^-$ (1)

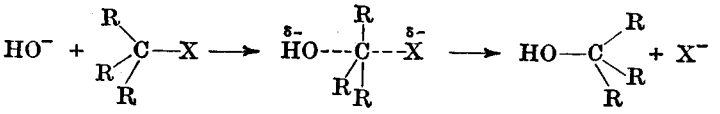
Hughes *et al.* (1935) studied (*a*) the interchange reaction of (+)-2-iodo-octane with radioactive iodine (as NaI*) in acetone solution, and (*b*) the racemisation of (+)-2-iodo-octane by ordinary sodium iodide under the same conditions. These reactions were shown to take place by the S_N2 mechanism, and the rate of racemisation was shown to be twice the rate of radioactive exchange, *i.e.*, every iodide–iodide* displacement is always accompanied by inversion. (Suppose there are n molecules of optically active iodo-octane. When $n/2$ molecules have exchange with I* and in doing so have been inverted, racemisation is now complete although the exchange has taken place with only *half* of the total number of molecules.) Thus this experiment leads to the *assumption* that inversion always occurs in the S_N2 mechanism. This is fully supported by other experimental work, *e.g.*, Hughes *et al.* (1936, 1938) studied the reaction of optically active α-bromoethylbenzene and α-bromopropionic acid with radioactive bromide ions, and again found that the rates of exchange (of bromide ions) and inversion were the same.

Thus the Walden inversion affords a means of studying the mechanism of substitution reactions. If complete inversion occurs, the mechanism is S_N2, or conversely, if the mechanism is known to be S_N2 (by, *e.g.*, kinetic data), complete inversion will result. This is the stereokinetic rule for S_N2 reactions, and its use thus offers a means of correlating configurations.

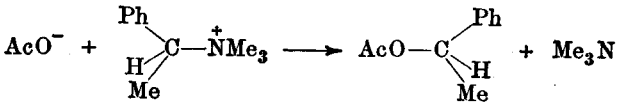
The essential problem that now arises is the consideration of the forces that determine the direction of attack, since the S_N2 mechanism might conceivably have taken place with retention as follows:

$$RX + OH^- \longrightarrow R\begin{matrix}\diagup X^{\delta-}\\ \diagdown OH^{\delta-}\end{matrix} \longrightarrow ROH + X^- \qquad (2)$$

Polanyi *et al.* (1932) suggested that the polarity of the C—X bond causes the negative ion (such as OH^-) to approach the molecule RX from the side *remote* from X; this is *end-on* attack:



Hughes and Ingold (1937), however, suggested from quantum-mechanical arguments that, independently of the above electrostatic repulsions, the minimum energy of activation results when the attacking ion approaches from a direction that would lead to inversion. Furthermore, these authors believe that the quantum-mechanical forces are more powerful than the electrostatic forces. There is much evidence to support this, *e.g.*, if electrostatic forces were the only or the predominating factor, then attack by a negatively charged nucleophilic reagent on a compound in which the displaced group has a positive charge would be expected to occur with retention (equation 2). In practice, however, inversion is still obtained, *e.g.*, the acetoxyl ion attacks the (+)-trimethyl-α-phenylethylammonium ion to give inversion (Snyder *et al.*, 1949):



A point of interest about the S_N2 reaction is that there are *four* electrostatically distinct types:

		Reagent	*Substrate*
1.	$Y^- + RX \longrightarrow YR + X^-$	negative	neutral
2.	$Y^- + RX^+ \longrightarrow YR + X$	negative	positive
3.	$Y + RX \longrightarrow YR^+ + X^-$	neutral	neutral
4.	$Y + RX^+ \longrightarrow YR^+ + X$	neutral	positive

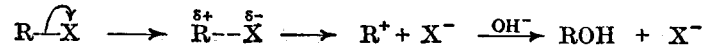
The stereokinetic rule for S_N2 reactions is well established for only reactions of type 1. Hughes, Ingold *et al.* (1960) have also shown that the rule applies to type 2, *e.g.*, the reaction between a sulphonium iodide and sodium azide (*cf.* Snyder's work):

$$CHMePh{\cdot}SMe_2^+ + N_3^- \longrightarrow CHMePh{\cdot}N_3 + Me_2S$$

These authors have also demonstrated that type 4 proceeds by the S_N2 mechanism, *e.g.*, with a sulphonium nitrate:

$$Me_3N + MeSMe_2^+ \longrightarrow Me_3NMe^+ + Me_2S$$

Now let us consider the S_N1 mechanism.



When the reaction proceeds by this mechanism, then inversion and retention (racemisation) will occur, the amount of each depending on various factors. The carbonium ion is flat (trigonal hybridisation), and hence attack by the nucleophilic reagent can take place equally well on either side, *i.e.*, equal amounts of the (+)- and (−)-forms will be produced; this is racemisation. One can expect complete racemisation only if the carbonium ion has a sufficiently long life; this is favoured by low reactivity of the carbonium ion and low concentration of the nucleophilic reagent. However, during the actual ionisation step, the retiring group will "protect" the carbonium ion from attack on that side, *i.e.*, there is a shielding effect, and this encourages an end-on attack on the other side, thereby leading to

inversion. An example of this type is the following. Bunton *et al.* (1955) studied the reaction of ^{18}O-enriched water on optically active *s*-butanol in aqueous perchloric acid, and found that the overall rate of racemisation is twice that of the oxygen exchange. Thus every oxygen exchange causes complete inversion of configuration (*cf.* the iodide–iodide* exchange described above). Bunton proposed the following mechanism to explain these results:

$$\mathrm{EtMeCHOH} + \mathrm{H^+} \underset{\text{fast}}{\overset{\mathrm{HClO_4}}{\rightleftharpoons}} \mathrm{EtMeCHOH_2^+} \tag{3}$$

$$\mathrm{EtMeCHOH_2^+} \overset{\text{slow}}{\rightleftharpoons} \mathrm{EtMe\overset{\delta+}{C}H\text{---}\overset{\delta+}{O}H_2} \tag{4}$$

$$\mathrm{H_2O^* + EtMe\overset{\delta+}{C}H\text{---}\overset{\delta+}{O}H_2} \overset{\text{fast}}{\rightleftharpoons} \mathrm{\overset{\delta+}{H_2O^*}\text{---}EtMeCH\text{---}\overset{\delta+}{O}H_2}$$

$$\overset{\text{fast}}{\rightleftharpoons} \mathrm{H_2\overset{+}{O}^*\text{—}CHMeEt + H_2O} \tag{5}$$

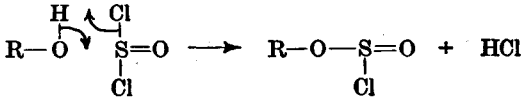
$$\mathrm{H_2\overset{+}{O}^*\text{—}CHMeEt} \overset{\text{fast}}{\rightleftharpoons} \mathrm{HO^*\text{—}CHMeEt + H^+} \tag{6}$$

(5) occurs before the OH_2^+ has completely separated in (4), and so this side is shielded and the H_2O^* is forced to attack on the other side as shown; the result is thus inversion. The above reaction proceeds by the S_N1 mechanism since (4) is the rate-determining step (only *one* molecule is undergoing covalency change in this step). Had the reaction been S_N2, complete inversion would still have been obtained. It was shown, however, that the reaction rate was independent of the concentration of H_2O^*. The mechanism is therefore S_N1, since had it been S_N2, the kinetic expression would require the concentration of the H_2O^*:

$$\mathrm{H_2O^* + EtMeCHOH_2^+} \overset{\text{slow}}{\rightleftharpoons} \mathrm{\overset{\delta+}{H_2O^*}\text{---}EtMeCH\text{---}\overset{\delta+}{O}H_2} \xrightarrow{\text{fast}} \mathrm{H_2\overset{+}{O}^*\text{—}CHMeEt + H_2O}$$

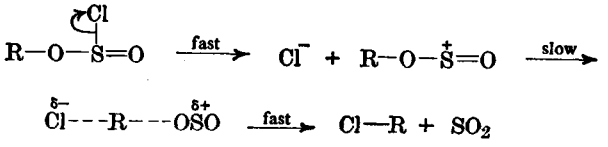
The stereochemical course of S_N1 reactions may also be affected by neighbouring group participation (see, *e.g.*, §6a).

§5. The S_Ni mechanism. Another important S_N reaction is the S_Ni type (substitution, nucleophilic, internal). The reaction between thionyl chloride and alcohols has been studied extensively. A well-examined example is the alcohol α-phenylethanol, PhCHOHMe; this is an *arylmethanol*, and according to Hughes, Ingold *et al.* (1937), the first step is the formation of a chlorosulphinate. No inversion occurs at this stage (which is a four-centre reaction); in the following equations, R = PhMeCH-:

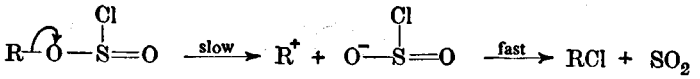


This chlorosulphinate could then form α-chloroethylbenzene by one or more of the following mechanisms:

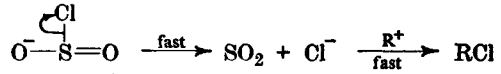
(i) **S_N2.** This occurs with inversion.



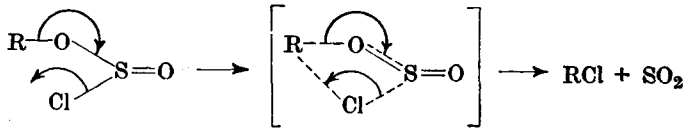
(ii) **S_N1.** This occurs with inversion and retention (racemisation).



The second stage may possibly be:



(iii) S_Ni. This occurs with retention (the reaction is effectively a four-centre type).



In practice, the α-chloroethylbenzene obtained has almost complete retention of configuration, and consequently the mechanism must be S_Ni. A point of interest here is that it is apparently difficult to postulate the nature of the transition state in this mechanism.

When α-phenylethanol and thionyl chloride react in the presence of pyridine, the α-chloroethylbenzene obtained now has the inverted configuration (Hughes, Ingold *et al.*, 1937). The explanation offered is that the S_N2 mechanism is operating, the substrate now being a pyridine complex:

$$ROSOCl + C_5H_5N \longrightarrow Cl^- + ROSO\overset{+}{N}C_5H_5 \longrightarrow$$
$$\overset{\delta-}{Cl}\cdots R\cdots\overset{\delta-}{O}SO\overset{+}{N}C_5H_5 \longrightarrow Cl{-}R + SO_2 + C_5H_5N$$

Optically active α-phenylethanol reacts with phosphorus trichloride, phosphorus pentachloride, and phosphoryl chloride, in the presence or absence of pyridine, and with hydrochloric acid, to give the *inverted* chloride. Thus all these proceed by the S_N2 mechanism. It is reasonable to assume that the chloride ion attacks some intermediate other than a pyridinium ion, since inversion occurs whether pyridine is present or absent.

§6. Participation of neighbouring groups in nucleophilic substitutions. So far, we have discussed polar effects (inductive and resonance) and steric effects on the rates and mechanisms of reactions. In recent years it has been found that another factor may also operate in various reactions. This factor is known as *neighbouring group participation*. Here we have a group attached to the carbon atom *adjacent* to the carbon atom where nucleophilic substitution occurs and, during the course of the reaction, becomes bonded or partially bonded to the reaction centre. Thus the rate and/or the stereochemistry of a reaction may be affected by this factor. When a reaction is accelerated by neighbouring group participation, that reaction is said to be *anchimerically assisted* (Winstein *et al.*, 1953). For anchimeric assistance to occur, the neighbouring group, which behaves as a nucleophilic reagent, must be suitably placed stereochemically with respect to the group that is ejected. This is the *trans*-configuration, and in this configuration the conditions for intramolecular displacement are best. Neighbouring group participation is also of great importance in the 1,2-shifts (see Vol. I; see also §2h. VI).

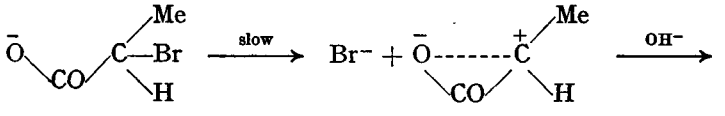
§6a. Neighbouring carboxylate anion. Hughes, Ingold *et al.* (1937) studied the following reaction of methyl D-α-bromopropionate:

$$Me{\cdot}CHBr{\cdot}CO_2Me \longrightarrow Me{\cdot}CH(OMe){\cdot}CO_2Me$$

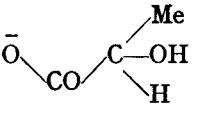
With concentrated methanolic sodium methoxide, the reaction was shown to be S_N2, and the product was L-methoxy ester (100 per cent. inversion). Under these conditions, the nucleophilic reagent is the methoxide ion, and the reaction is first order with respect to both methoxide ion and ester.

When the ester was subjected to methanolysis, *i.e.*, methanol was the solvent (no methoxide ion now present), the product was again L-methoxy ester (100 per cent. inversion). The reaction was now first order (*i.e.*, pseudo first order), but still S_N2, the nucleophilic reagent being the solvent molecules of methanol. When the sodium salt of D-α-bromopropionic acid was hydrolysed in dilute sodium hydroxide solution, the mechanism was shown to be S_N1, and the product was now D-α-hydroxypropionate anion (100 per cent. retention). In concentrated sodium hydroxide solution, however, the mechanism was S_N2 (due to the high concentration of the hydroxide ion), and the product was L-α-hydroxypropionate anion (100 per cent. inversion).

Hughes and Ingold have proposed the following explanation for the retention experiment. The first step is ionisation to a carbonium ion in which the negatively charged oxygen atom forms a " weak electrostatic bond " with the positively charged carbon atom on the side remote from that where the bromide ion is expelled. Thus this remote side is " protected " from attack by the hydroxide ion, which is consequently forced to attack from the same side as that of the expelled bromide ion, thereby leading to retention of configuration.

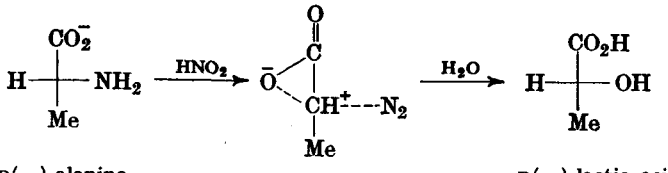


protection



retention

Hughes, Ingold *et al.* (1950) showed that the deamination of optically active alanine by nitrous acid gave an optically active lactic acid with retention of configuration. This is also explained by neighbouring group participation of the α-carboxylate anion:

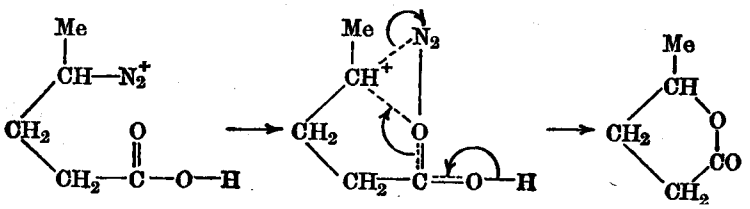


D(−)-alanine D(−)-lactic acid

This effect of neighbouring group participation is supported by the fact that in the absence of the α-carboxylate ion, Hughes, Ingold *et al.* observed that there was an overall inversion of configuration (with much racemisation) in the deamination of simple optically active amines, and explained this as being due to asymmetrical shielding of the carbonium ion by the expelled nitrogen.

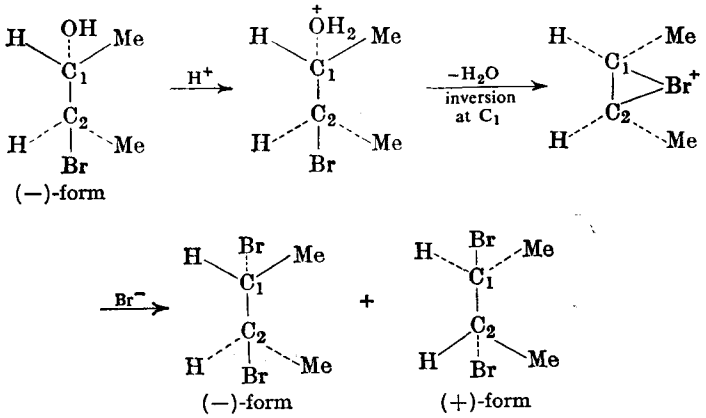
As we have seen above, neighbouring group participation involves a group on the *adjacent* carbon atom. Austin *et al.* (1961) have offered an example where the " neighbouring group " is on the γ-carbon atom. These authors have shown that there is 80 per cent. retention of configuration in the deamination of γ-aminovaleric acid; the product is a lactone. Thus a " free " carbonium ion is not involved in the formation of the lactone.

The authors suggest the following mechanism, neighbouring group participation occurring as shown:

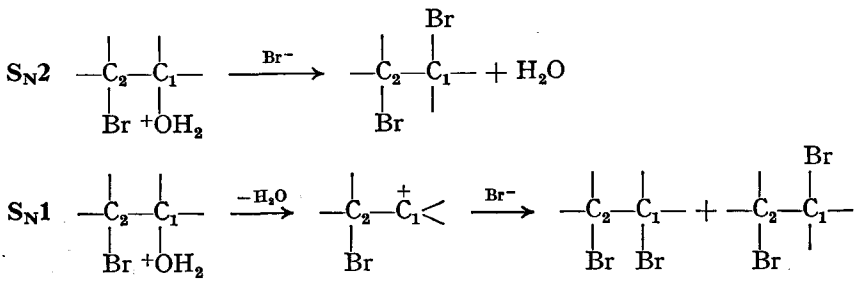


Thus the oxygen atom of the γ-carboxyl group enters the site, originally occupied by the amino-group, by an S_Ni mechanism.

§6b. Neighbouring halogen atoms. Brominium (bromonium) ions were first proposed by Roberts and Kimball (1937) as intermediates in the addition of bromine to olefins (see §5. IV). The existence of this cyclic brominium ion has been demonstrated by Winstein and Lucas (1939), who found that the action of fuming hydrobromic acid on (−)-*threo*-3-bromobutan-2-ol gave (±)-2,3-dibromobutane.



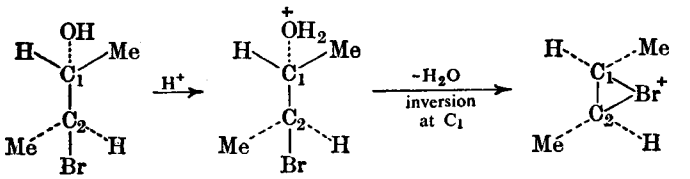
If no neighbouring group participation of bromine occurred in the above reactions, then if the reaction were S_N2, complete inversion would have



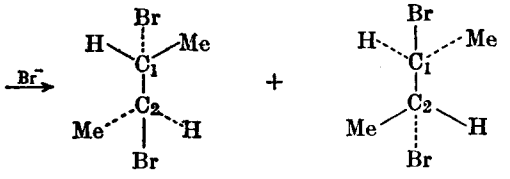
occurred only at C_1. If the reaction were the ordinary S_N1, the C_1 would have been a classical carbonium ion (flat), and so inversion and retention (racemisation) would have occurred only at C_1. Since either retention of inversion occurs at *both* C_1 and C_2, the results are explained by neighbouring group participation of the bromine atom.

The above mechanism also explains the formation of *meso*-2,3-dibromobutane by the action of fuming hydrobromic acid on optically active *erythro*-

3-bromobutan-2-ol (I); (II) and (III) are identical and correspond to the *meso*-form.

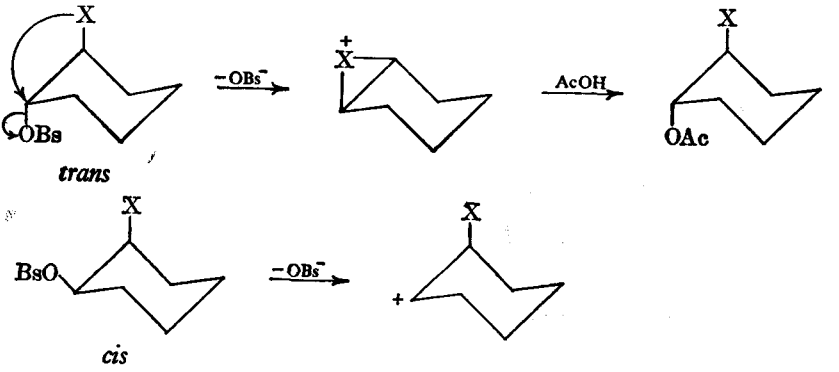


I



II III

There is evidence that all the halogen atoms can form cyclic ions and offer anchimeric assistance, *e.g.*, Winstein *et al.* (1948, 1951) studied the acetolysis of *cis*- and *trans*-2-halogeno-*cyclo*hexyl brosylates (*i.e.*, *p*-bromobenzenesulphonates; this group is often written as OBs):

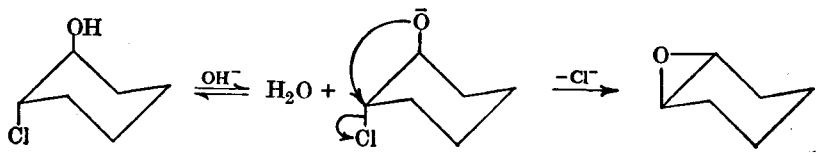


In the absence of neighbouring group participation, the rates would be expected to be about the same. If participation occurs, then this is readily possible in the *trans*-isomer (1*a* : 2*a*) by attack of X at the *rear* of the ejected OBs^- ion, but this is not so for the *cis*-isomer (1*e* : 2*a*; see §11. IV). The rate ratios observed were:

trans/cis: X = I, $2{\cdot}7 \times 10^6/1$; X = Br, 800/1; X = Cl, 3·8/1.

Thus iodine affords the greatest anchimeric assistance and chlorine the least (see also §6c).

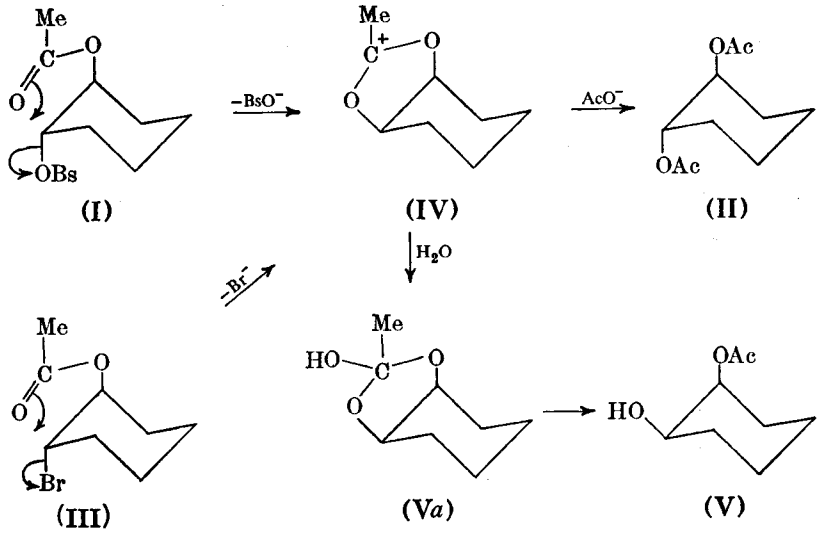
§6c. Neighbouring hydroxyl group. Bartlett (1935) showed that alkali converts *trans*-2-chloro*cyclo*hexanol into *cyclo*hexene oxide, and proposed a mechanism in which an alkoxide ion is formed first and this then ring-closes with ejection of the chloride ion:



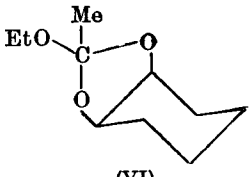
Bergvist (1948) showed that this reaction proceeds more than 100 times as fast as that when the *cis*-compound is used. Here again, the *trans*-form permits ready attack at the rear of the chloride ion whereas the *cis*-isomer does not (*cf.* §6b). The fact that the *cis*-form does react may be explained by assuming that the reaction proceeds *via* the *trans*-form, *i.e.*, the former is first converted into the latter. This requires energy of activation and consequently the reaction for the *cis*-form is slowed down (*cf.* §6d).

Another example of neighbouring hydroxyl participation is the conversion of sugars into epoxy-sugars (see §9. VII).

§6d. Neighbouring acetoxyl group. Winstein *et al.* (1942, 1943) showed that a neighbouring acetoxyl group leads to the formation of an acetoxonium ion. *trans*-2-Acetoxy*cyclo*hexyl brosylate (I) forms *trans*-1,2-diacetoxy*cyclo*hexane (II) when treated with silver acetate, and the same product (II) is obtained when the starting material is *trans*-2-acetoxy*cyclo*hexyl bromide (III). The authors believe that the course of the reaction, based on the stereochemical evidence, proceeds through the *same* acetoxonium ion (IV). This mechanism is supported by the fact that in each case, when the reaction was carried out in the presence of a small amount of water, the product was now the monoacetate of *cis-cyclo*hexane-1,2-diol(V); some diacetate of this *cis*-diol was also obtained.



Further support for the formation of (IV) is afforded by the fact that the *cis*-isomers of (I) and (III) undergo the same reactions but at much slower rates; anchimeric assistance can readily operate in the *trans*-form. It is possible that for the *cis*-forms, the reactions proceed *via* the *trans*-forms, *i.e.*, the *cis*-form is first converted into the *trans*. This requires energy of activation and consequently the reactions with the *cis*-forms are slowed down. The formation of the intermediate (V*a*) is supported by the



(VI)

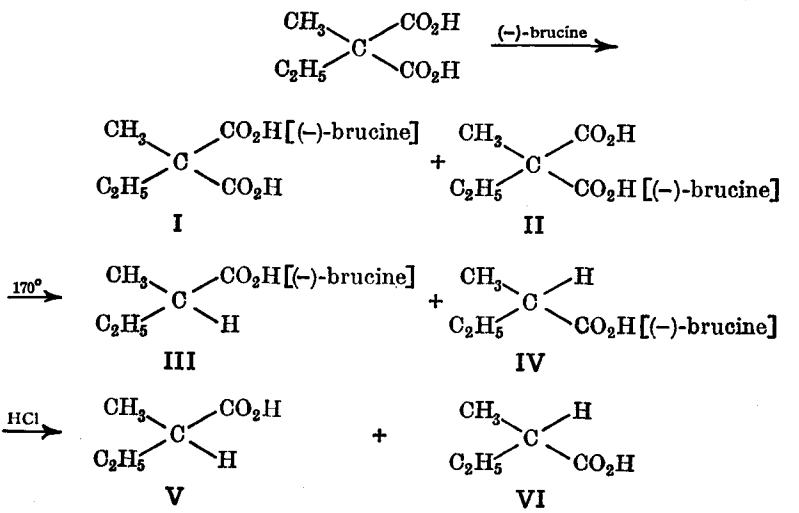
fact that when the solvolysis of (I) is carried out in ethanol, (VI) is obtained (Winstein *et al.*, 1943).

ASYMMETRIC SYNTHESIS

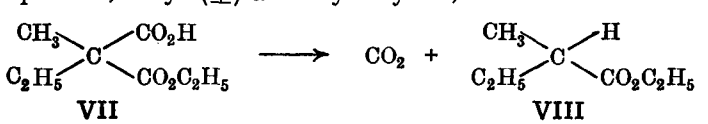
§7. Partial asymmetric synthesis. Partial asymmetric synthesis may be defined as a method for preparing optically active compounds from symmetrical compounds by the intermediate use of optically active compounds, but without the necessity of resolution (Marckwald, 1904). In ordinary laboratory syntheses, a symmetrical compound always produces the racemic modification (§7a. II).

The first asymmetric synthesis was carried out by Marckwald (1904), who prepared an active (—)-valeric acid (lævorotatory to the extent of about 10 per cent. of the pure compound) by heating the half-brucine salt of ethylmethylmalonic acid at 170°.

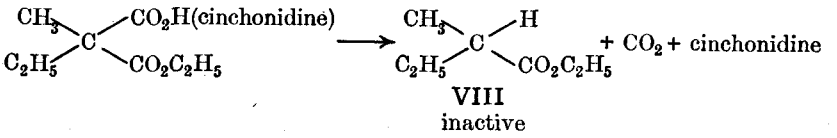
I and II are diastereoisomers; so are III and IV. V and VI are enantiomorphs, and since the mixture is optically active, they must be present in unequal amounts. Marckwald believed this was due to the different rates of decomposition of diastereoisomers I and II, but according to Eisenlohr and Meier (1938), the half-brucine salts I and II are not present in equal amounts in the solid form (as thought by Marckwald). These authors suggested that as the less soluble diastereoisomer crystallised out (during



evaporation of the solution), some of the more soluble diastereoisomer spontaneously changed into the less soluble diastereoisomer to restore the equilibrium between the two; thus the final result was a mixture of the half-brucine salt containing a larger proportion of the less soluble diastereoisomer. If this be the explanation, then we are dealing with an example of asymmetric transformation and not of asymmetric synthesis (see §10. II). Further work, however, has shown that Marckwald had indeed carried out an asymmetric synthesis. Kenyon and Ross (1951) decarboxylated optically active ethyl hydrogen ethylmethylmalonate, VII, and obtained an optically inactive product, ethyl (±)-α-methylbutyrate, VIII.

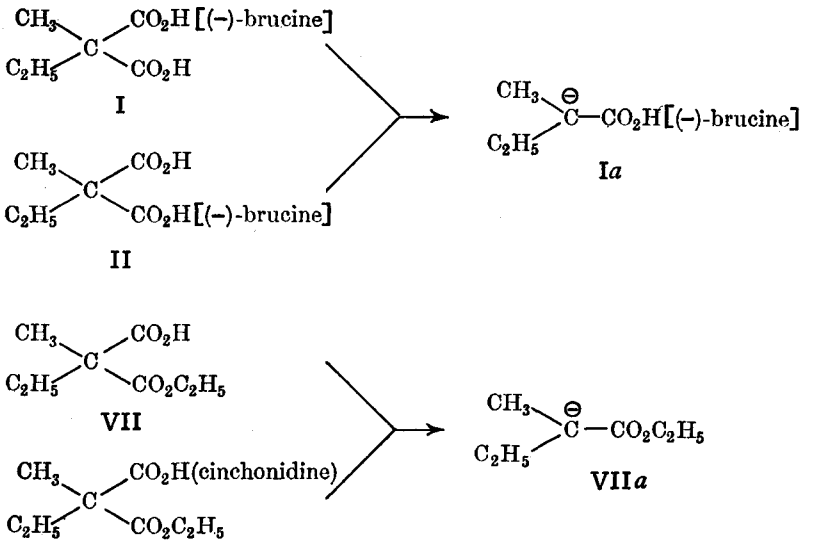


These authors (1952) then decarboxylated the cinchonidine salt of VII, and still obtained the optically inactive product VIII.

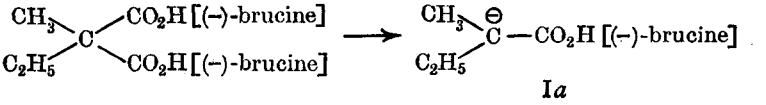


VIII
inactive

Kenyon and Ross suggest the following explanation to account for their own experiments and for those of Marckwald. Decarboxylation of diastereoisomers I and II takes place *via* the formation of the same carbanion I*a*, and decarboxylation of VII and its cinchonidine salt *via* VII*a*.



Combination of carbanion I*a* with a proton will produce diastereoisomers III and IV in different amounts, since, in general, diastereoisomers are formed at different rates (§7*b*. II). On the other hand, carbanion VII*a* will give equimolecular amounts of the enantiomorphs of VIII. If the formation of optically active α-methylbutyric acid (V and VI) were due to different rates of decarboxylation of III and IV (Marckwald's explanation) or to partial asymmetric transformation during crystallisation (Eisenlohr and Meier's explanation), then these effects are nullified if Kenyon's explanation is correct, since the intermediate carbanion is the *same* for both diastereoisomers. Thus, if the asymmetric transformation theory were correct, then decarboxylation of the *dibrucine* salt of ethylmethylmalonic acid to α-methylbutyric acid should give an optically inactive product, since only one type of crystal is now possible (asymmetric transformation is now impossible).



On the other hand, if the carbanion I*a* is an intermediate in this decomposition, it is still possible to obtain an optically active product. Kenyon and Ross did, in fact, obtain a lævorotatory product.

McKenzie (1904) carried out a number of partial asymmetric syntheses by reduction of the keto group in various keto-esters in which the ester group contained an asymmetric group, *e.g.*, benzoylformic acid was esterified with (−)-menthol, the ester reduced with aluminium amalgam, and the resulting product saponified; the mandelic acid so obtained was slightly lævorotatory.

$$C_6H_5{\cdot}CO{\cdot}CO_2H + (-)\text{-}C_{10}H_{19}OH \longrightarrow C_6H_5{\cdot}CO{\cdot}CO_2C_{10}H_{19} + H_2O \xrightarrow{Al/Hg}$$
$$C_6H_5{\cdot}CHOH{\cdot}CO_2C_{10}H_{19} \xrightarrow{H_2O} C_6H_5{\cdot}CHOH{\cdot}CO_2H + (-)\text{-}C_{10}H_{19}OH$$
$$(-)\text{-rotation}$$

Similarly, the pyruvates of (−)-menthol, (−)-pentyl alcohol and (−)-borneol gave an optically active lactic acid (slightly lævorotatory) on reduction.

$$CH_3{\cdot}CO{\cdot}CO_2R(-) \xrightarrow{[H]} CH_3{\cdot}CHOH{\cdot}CO_2R(-) \xrightarrow{H_2O}$$
$$CH_3{\cdot}CHOH{\cdot}CO_2H + (-)\text{-ROH}$$
$$(-)\text{-rotation}$$

McKenzie (1904) also obtained similar results with Grignard reagents, *e.g.*, the (−)-menthyl ester of benzoylformic acid and methylmagnesium iodide gave a slightly lævorotatory atrolactic acid.

$$C_6H_5{\cdot}CO{\cdot}CO_2C_{10}H_{19} + CH_3{\cdot}MgI \longrightarrow C_6H_5{\cdot}C(OMgI)(CO_2C_{10}H_{19})(CH_3)$$

$$\xrightarrow{H_2O} C_6H_5{\cdot}C(OH)(CO_2H)(CH_3) + (-)\text{-}C_{10}H_{19}OH$$

(−)-rotation

Turner *et al.* (1949) carried out a Reformatsky reaction (see Vol. I) using acetophenone, (−)-menthyl bromoacetate and zinc, and obtained a dextrorotatory β-hydroxy-β-phenylbutyric acid.

$$(C_6H_5)(CH_3)C{=}O + Zn + CH_2Br{\cdot}CO_2C_{10}H_{19} \longrightarrow$$

$$(C_6H_5)(CH_3)C(OZnBr)(CH_2{\cdot}CO_2C_{10}H_{19}) \longrightarrow (C_6H_5)(CH_3)C(OH)(CH_2{\cdot}CO_2H)$$

(+)-rotation

Reid *et al.* (1962) have also used aldehydes in the Reformatsky reaction, *e.g.*, benzaldehyde gave a lævorotatory β-hydroxy-β-phenylpropionic acid. Jackman *et al.* (1950) reduced *tert.*-butyl *n*-hexyl ketone with aluminium (+)-1 : 2 : 2-trimethylpropoxide at 200°, and obtained a slightly lævorotatory alcohol.

$$(CH_3)_3C{\cdot}CO{\cdot}C_6H_{13} \xrightarrow{[(CH_3)_2C{\cdot}CH(CH_3)O]_3Al} (CH_3)_3C{\cdot}CHOH{\cdot}C_6H_{13}$$
$$(-)\text{-rotation}$$

Another example of asymmetric synthesis involving the use of a Grignard reagent is the *reduction* of 3 : 3-dimethylbutan-2-one into a dextrorotatory

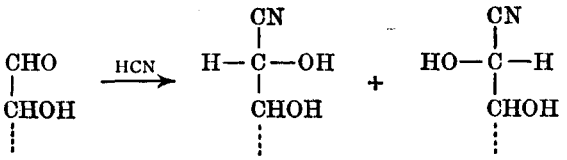
$$(CH_3)_3C{\cdot}CO{\cdot}CH_3 \xrightarrow{(+)-CH_3{\cdot}CH_2{\cdot}CH(CH_3){\cdot}CH_2MgCl} (CH_3)_3C{\cdot}CHOH{\cdot}CH_3$$
$$(+)\text{-rotation}$$

3 : 3-dimethylbutan-2-ol by means of (+)-2-methylbutylmagnesium chloride (Mosher *et al.*, 1950; see also Vol. I for abnormal Grignard reactions).

Bothner-By (1951) reduced butanone with lithium aluminium hydride in the presence of (+)-camphor, and thereby obtained (+)-*iso*borneol (from the camphor) and a small amount of a dextrorotatory butan-2-ol. The reducing agent in this case is a complex aluminohydride ion formed from lithium aluminium hydride and camphor, *e.g.*, $Al(OR)H_3^-$.

$$CH_3{\cdot}CO{\cdot}C_2H_5 \xrightarrow[(+)-\text{camphor}]{LiAlH_4} CH_3{\cdot}CHOH{\cdot}C_2H_5$$
(+)-rotation

It has already been pointed out that a molecule containing one asymmetric carbon atom gives rise to a pair of diastereoisomers in *unequal* amounts when a second asymmetric carbon atom is introduced into the molecule (§7b. II). In general, if a new asymmetric centre is introduced into a molecule which is already asymmetric, the asymmetric part of the molecule influences the configuration formed from the symmetrical part of the molecule, the two diastereoisomers being formed in unequal amounts, *e.g.*, the Kiliani reaction (see also Vol. I).

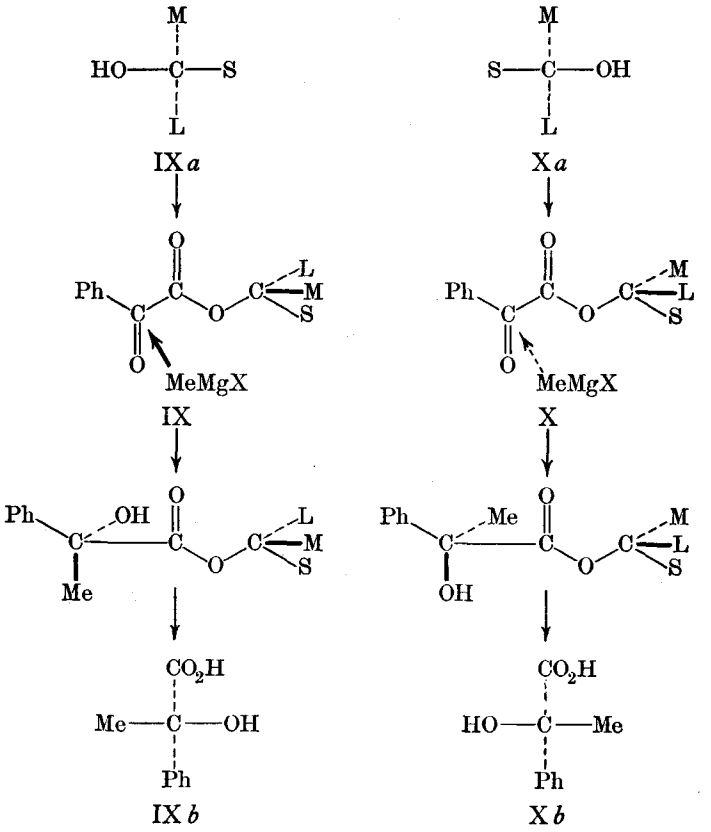


Prelog *et al.* (1953) have studied, by means of conformational analysis, the steric course of the addition of Grignard reagents to benzoylformic (phenylglyoxylic) esters of asymmetric alcohols. If the letters S, M and L refer respectively to small, medium and large groups attached to the carbinol carbon atom of the asymmetric alcohol, then the general reaction may be written:

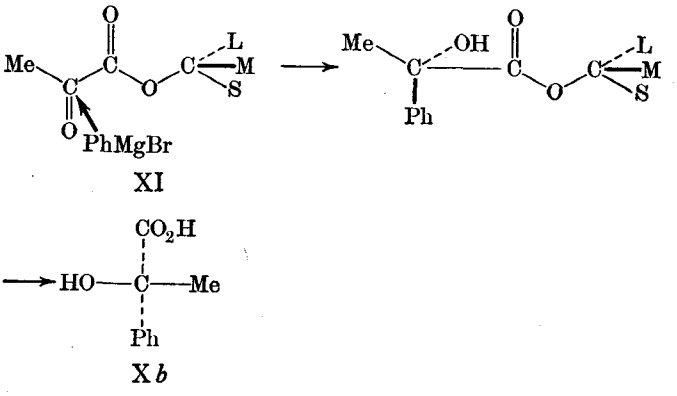
$$C_6H_5{\cdot}CO{\cdot}CO_2CSML \xrightarrow{RMgX} C_6H_5{\cdot}CR(OH){\cdot}CO_2CSML \xrightarrow{\text{hydrol.}} C_6H_5{\cdot}CR(OH)CO_2H$$

Prelog *et al.* found that the configuration of the asymmetric carbon atom in the stereoisomer that predominated in this reaction could be correlated with that of the carbinol carbon of the alcohol. The basis of this correlation was the assumption that the Grignard reagent attacks the carbon atom (of the ketone group) preferentially from the less hindered side. This necessitates a consideration of the possible conformations of the ester molecule. The authors considered that the most stable conformation of the ester was the one in which the two carbonyl groups are planar and *trans* to each other, with the smallest group lying in this plane and the other two groups skew. Furthermore, with the groups on the carbinol atom of the alcohol arranged in the staggered conformation with respect to the rest of the molecule, then IX and X will be the conformations of the esters with the enantiomorphous alcohol residues IX *a* and X *a* respectively (thick lines represent groups in front of the plane, broken lines groups behind, and ordinary lines groups in the plane). Thus, with L behind, methylmagnesium halide attacks preferentially from the front (IX); and with L in front, the attack is from behind (X). The α-hydroxyacid obtained from IX is IX *b*, and that from X is X *b*. IX *b* and X *b* are enantiomorphs and hence the configuration of the new asymmetric centre is related to that of the adjacent asymmetric centre in the original molecule. Thus for the same keto-acid and the same Grignard reagent, and using different optically active alcohols belonging to the same configurational series, the product should contain excess of α-hydroxyacids with the same sign of rotation. This has been shown to be so in practice, *e.g.*, (−)-menthol and (−)-borneol

are both configurationally related to L(−)-glyceraldehyde, and both lead to a predominance of the (−)-hydroxyacid. On the other hand, if the keto-acid is pyruvic acid and the Grignard reagent phenylmagnesium bromide, the (+)-hydroxyacid should predominate in the product (this method of preparation produces an interchange of the positions of the phenyl and methyl groups, thereby leading to the formation of the enantiomorph). This can

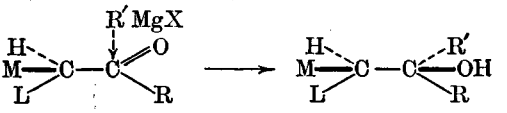


be seen from the following equation: starting with the pyruvic ester XI in which the configuration of the alcohol is IX *a*, the product would be X *b*.

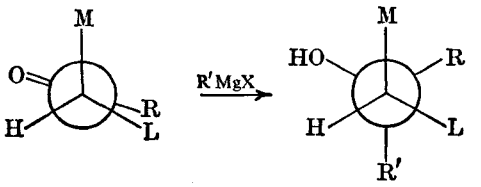


These results have been obtained in practice. Thus, when the configuration of the active alcohol is known, it is possible to deduce the configuration of the α-hydroxyacid obtained in excess. This method has been used to determine the configuration of hydroxyl groups in steroids.

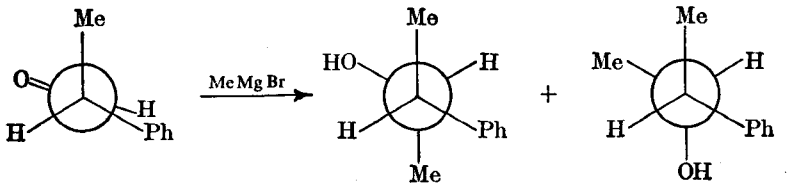
Cram *et al.* (1952) have also dealt with asymmetric syntheses in which the molecule contains an asymmetric centre that belongs to the molecule, *i.e.*, remains in the molecule (*cf.* the Kiliani reaction mentioned above). As a result of their work, these authors have formulated the rule of " steric control of asymmetric induction ". This is: " In non-catalytic reactions of the type shown, that diastereoisomer will predominate which would be formed by the approach of the entering group from the *least hindered side* of the double bond when the rotational conformation of the C—C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric centre." Thus :



or, using the Newman projection formulæ:



An example of this type of reaction is the reaction between phenylpropionaldehyde (M = Me, L = Ph) and methylmagnesium bromide (R′ = Me); two products can be formed, *viz.*, XII the (*erythro*-compound) and XIII (the *threo*-compound):



XII XIII

According to the above rule, XII should predominate; this has been found to be so in practice.

Cram's rule does not give the correct stereochemical prediction when one of the groups (*e.g.*, hydroxyl) attached to the carbon atom *alpha* to the carbonyl group is capable of chelating with a metal atom in the reagent, unless this chelating group is " medium " in effective bulk.

The influence of enzymes on the steric course of reactions has also been investigated, *e.g.*, Rosenthaler (1908) found that emulsin converted benzaldehyde and hydrogen cyanide into dextrorotatory mandelonitrile which was almost optically pure. It has been found that in most enzymic reactions the product is almost 100 per cent. of one or other enantiomorph. Enzymes are proteins and optically active (see also §12. XIII), but since they are so " one-sided " in their action, it appears likely that the mechanism of the reactions in which they are involved differs from that of partial asymmetric

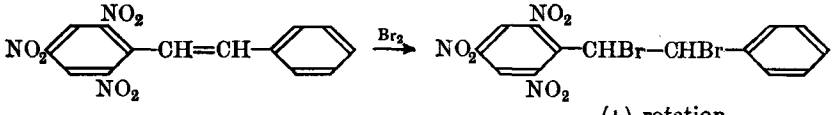
syntheses where enzymes are not used. It has been suggested that enzymes are the cause of the formation of optically active compounds in plants. Although this is largely true, the real problem is: How were the optically active enzymes themselves produced? Ferreira's work [§10(viii). II], however, shows that optically active compounds may possibly be produced in living matter by activation of a racemic modification. This theory appears to be superior to that of the formation of optically active compounds by the action of naturally polarised light (see following section).

§8. Absolute asymmetric synthesis. Cotton (1896) found that dextro- and lævocircularly polarised light was unequally absorbed by enantiomorphs, provided the light has a wavelength in the neighbourhood of the characteristic absorption bands of the compound. This phenomenon is known as the **Cotton effect** or **circular dichroism** (*cf.* §2. II).

It has been suggested that circularly polarised light produced the first natural active compounds, and to support this theory, racemic modifications have been irradiated with circularly polarised light and attempts made to isolate one enantiomorph. There was very little success in this direction until W. Kuhn and Braun (1929) claimed to have obtained a small rotation in the case of ethyl α-bromopropionate. The racemic modification of this compound was irradiated with right- and left-circularly polarised light (of wavelength 2800 A), and the product was found to have a rotation of + or −0·05°, respectively. Thus we have the possibility of preparing optically active products from inactive substances *without* the intermediate use of optically active reagents (*cf.* Ferreira's work). This type of synthesis is known as an **absolute asymmetric synthesis;** it is also known as an **absolute asymmetric decomposition.** The term asymmetric decomposition is also applied to reactions such as the formation of the (+)- and (−)-forms of αγ-di-1-naphthyl-αγ-diphenylallene (see §6. V) by the action of (+)- and (−)-camphorsulphonic acid on the symmetrical alcohol.

From 1930 onward, more conclusive evidence for absolute asymmetric syntheses has been obtained, *e.g.*, W. Kuhn and Knopf (1930) irradiated (±)-α-azidopropionic dimethylamide, $CH_3{\cdot}CHN_3{\cdot}CO{\cdot}N(CH_3)_2$, with right-circularly polarised light and obtained an undecomposed product with a rotation of +0·78°; with left-circularly polarised light, the undecomposed product had a rotation of −1·04°. Thus the (−)- or (+)-form is decomposed (photochemically) by right- or left-circularly polarised light, respectively. Similarly, Mitchell (1930) irradiated humulene nitrosite with right- and left-circularly polarised red light, and obtained slightly optically active products.

Davis and Heggie (1935) found that the addition of bromine to 2 : 4 : 6-trinitrostilbene in a beam of right-circularly polarised light gave a dextrorotatory product.



(+)-rotation

Small (+)-rotations were also observed when a mixture of ethyl fumarate and anhydrous hydrogen peroxide in ethereal solution was irradiated with right-circularly polarised light (Davis *et al.*, 1945).

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CHAPTER IV

GEOMETRICAL ISOMERISM

§1. Nature of geometrical isomerism. Maleic and fumaric acids both have the same molecular formula $C_4H_4O_4$, but differ in most of their physical and in many of their chemical properties, and neither is optically active. It was originally thought that these two acids were structural isomers; this is the reason for different names being assigned to each form (and to many other geometrical isomers). It was subsequently shown, however, that maleic and fumaric acids were not structural isomers, *e.g.*, both (i) are catalytically reduced to succinic acid; (ii) add one molecule of hydrogen bromide to form bromosuccinic acid; (iii) add one molecule of water to form malic acid; (iv) are oxidised by alkaline potassium permanganate to tartaric acid (the *stereochemical* relationships in reactions (ii), (iii) and (iv) have been ignored; they are discussed later in §5a). Thus both acids have the same structure, *viz.*, $CO_2H{\cdot}CH{:}CH{\cdot}CO_2H$. van't Hoff (1874) suggested that if we assume there is *no free rotation about a double bond*, two spatial arrangements are possible for the formula $CO_2H{\cdot}CH{:}CH{\cdot}CO_2H$, and these would account for the isomerism exhibited by maleic and fumaric acids. Using tetrahedral diagrams, van't Hoff represented a double bond by placing the tetrahedra edge to edge (Fig. 1). From a *mechanical* point of view, such

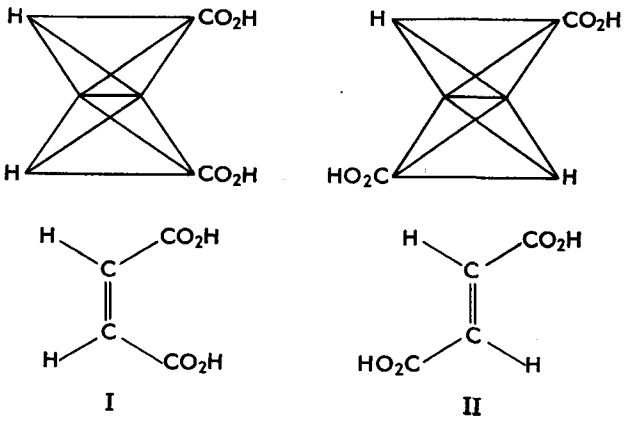


FIG. 4.1.

an arrangement would be rigid, *i.e.*, free rotation about the double bond is not to be expected. Furthermore, according to the above arrangement, the two hydrogen atoms and the two carboxyl groups are all in one plane, *i.e.*, the molecule is flat. Since a flat molecule is superimposable on its mirror image, maleic and fumaric acids are therefore not optically active (§2. II). As we shall see later, modern theory also postulates a planar structure for these two acids, but the reasons are very much different from those proposed by van't Hoff as described above (see also §3a. V).

The type of isomerism exhibited by maleic and fumaric acids is known as **geometrical isomerism** or ***cis-trans* isomerism.** One isomer is known as the *cis*-compound, and the other as the *trans*, the *cis*-compound being the one which (usually) has identical or similar atoms or groups, on the *same* side (see also §4). Thus molecule I is *cis*-butenedioic acid, and II is

trans-butenedioic acid. As will be shown later (§5), I is maleic acid and II fumaric acid.

Geometrical isomerism is exhibited by a wide variety of compounds, and they may be classified into three groups:

(i) Compounds containing a double bond: C=C, C=N, N=N.
(ii) Compounds containing a cyclic structure—homocyclic, heterocyclic and fused ring systems.
(iii) Compounds which may exhibit geometrical isomerism due to restricted rotation about a single bond (see §3. V for examples of this type).

§2. Rotation about a double bond. We have already seen that, theoretically, there is always some opposition to rotation about a *single* bond and that, in many cases, the opposition may be great enough to cause the molecule to assume some preferred conformation (§4a. II). When we consider the problem of rotation about a *double* bond, we find that there is always considerable opposition to the rotation. Let us first consider the simple case of ethylene; Fig. 2 (*a*) shows the energy changes in the molecule when one methylene group is rotated about the carbon–carbon double bond with the other methylene group at rest. Thus there are two *identical* favoured positions (one at 0° and the other at 180°), and the potential energy barrier is 40 kg.cal./mole. The examination of many olefinic compounds has shown that the potential energy barrier for the C=C bond varies with the nature of the groups attached to each carbon, *e.g.*,

$CH_2{=}CH_2$, 40 kg.cal./mole;
$C_6H_5{\cdot}CH{=}CH{\cdot}C_6H_5$, 42·8 kg.cal./mole;
$CH_3{\cdot}CH{=}CH{\cdot}CH_3$, 18 kg.cal./mole;
$CO_2H{\cdot}CH{=}CH{\cdot}CO_2H$, 15·8 kg.cal./mole.

Let us consider the case of maleic and fumaric acids in more detail. It can be seen from the diagram (Fig. 2 *b*) that there are *two* favoured positions, with the *trans*-form more stable than the *cis*, the energy difference between the two being 6–7 kg.cal./mole. The conversion of the *trans* to the *cis* requires 15·8 kg.cal. energy, but the reverse change requires about 10 kg.cal. (see also §6 for a further discussion of *cis-trans* isomerisation).

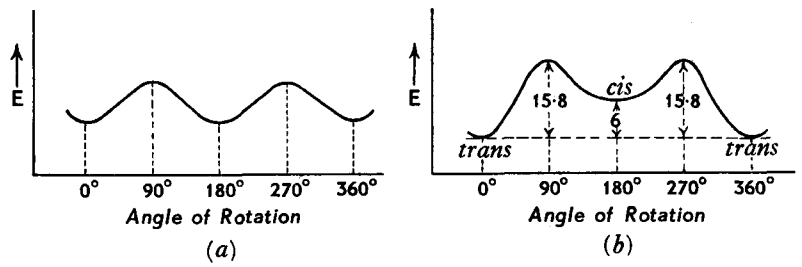


FIG. 4.2.

§3. Modern theory of the nature of double bonds. In the foregoing account of geometrical isomerism, the distribution of the carbon valencies was assumed to be tetrahedral (as postulated by van't Hoff). According to modern theory, the four valency bonds of a carbon atom are distributed tetrahedrally only in *saturated* compounds. In such compounds the carbon is in a state of *tetrahedral hybridisation*, the four sp^3 bonds being referred to as σ-bonds (see Vol. I, Ch. II). In olefinic compounds, however, the two carbon atoms exhibit the *trigonal* mode of hybridisation. In this condition there are three coplanar valencies (three σ-bonds produced from sp^2 hybrid-

isation), and the fourth bond (π-bond) at right angles to the trigonal hybrids (Fig. 3). π-Bonds, which appear to be weaker than σ-bonds, tend to overlap as much as possible in order to make the bond as strong as possible. Maximum overlap is achieved when the molecule is planar, since in this configuration the two p_z orbitals are parallel. Distortion of the molecule from the planar configuration decreases the overlap of the π-electrons, thereby weakening the π-bond; and this distortion can only be effected by supplying energy to the molecule. It is therefore this tendency to produce **maximum overlap of the π-electrons in the π-bond** that gives rise to resistance

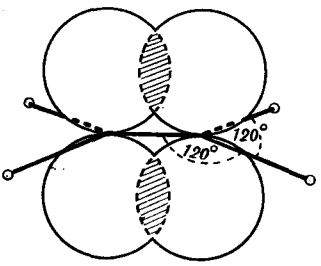


FIG. 4.3.

of rotation about a " double " bond. For simplicity we shall still represent a " double " bond by the conventional method, *e.g.*, C=C, but it should always be borne in mind that *one* of these bonds is a σ-bond (sp^2 bond), and the *other* is a π-bond perpendicular to the σ-bond. It is these π-electrons (*mobile electrons*) which undergo the electromeric and resonance effects. They are held less firmly than the σ-electrons and are more exposed to external influences; it is these π-electrons which are responsible for the high reactivity of unsaturated compounds.

In compounds containing a triple bond, *e.g.*, acetylene, the two carbon atoms are in a state of *digonal* hybridisation; there are two σ-bonds (sp bonds) and two π-bonds (one p_y and one p_z orbital), both perpendicular to the σ-bonds which are collinear (see Vol. I, Ch. II).

The above treatment of the double (and triple) bond is in terms of sp^2 (and sp) hybridisation and π-bonds. It is still possible, however, to use sp^3 hybridisation to describe carbon–carbon multiple bonds; this treatment gives rise to " banana-shaped " orbitals, *i.e.*, " bent " bonds (Fig. 4 ; see also Vol. I):

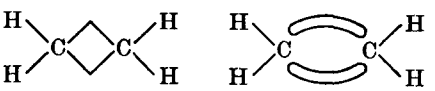
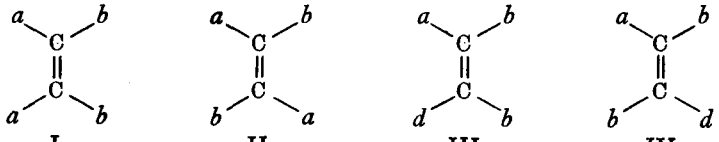


FIG. 4.4

This method of approach still produces a " rigid " molecule, and so again there is no free rotation about the double bond.

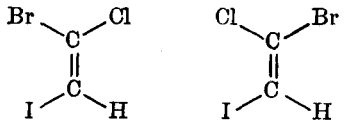
§4. Nomenclature of geometrical isomers. When geometrical isomerism is due to the presence of *one* double bond in a molecule, it is easy to name the geometrical isomers if two groups are identical, *e.g.*, in molecules I and II, I is the *cis*-isomer, and II the *trans*; similarly III is *cis*, and IV is *trans*. When, however, all four groups are different, nomenclature is more difficult. In this case it has been suggested that the prefixes *cis* and *trans* should indicate the disposition of the *first two* groups named, *e.g.*, the two stereoisomers of 1-bromo-1-chloro-2-iodoethylene, V and VI; V is *cis*-1-bromo-2-iodo-1-chloroethylene or *trans*-1-chloro-2-iodo-1-bromo-ethylene;

VI is *cis*-1-chloro-2-iodo-1-bromoethylene or *trans*-1-bromo-2-iodo-1-chloroethylene. On the other hand, since this method of nomenclature usually deviates from the rule of naming groups in alphabetical order, it has been



I *cis* II *trans* III *cis* IV *trans*

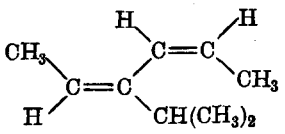
suggested that the groups corresponding to the prefix *cis* or *trans* should be italicised, thus V may be named *cis*-1-*bromo*-1-chloro-2-*iodo*ethylene and VI *trans*-1-*bromo*-1-chloro-2-*iodo*ethylene. This method, it must be admitted, would offer difficulties when the names are spoken.



V VI

Some pairs of geometrical isomers have trivial names, *e.g.*, maleic and fumaric acids, angelic and tiglic acids, etc. (*cf.* §1). Sometimes the prefix *iso* has been used to designate the *less* stable isomer, *e.g.*, crotonic acid (*trans*-isomer) and *iso*crotonic acid (*cis*-isomer; the *cis*-isomer is usually the less stable of the two; see §2). The use of *iso* in this connection is undesirable since it already has a specific meaning in the nomenclature of alkanes. The prefix *allo* has also been used to designate the less stable isomer (*cis*), *e.g.*, *allo*cinnamic acid.

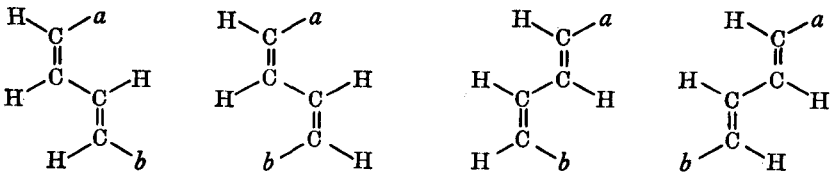
When geometrical isomers contain two or more double bonds, nomenclature may be difficult, *e.g.*, VII. In this case the compound is considered



VII

as a derivative of the longest chain which contains the maximum number of double bonds, the prefixes *cis* and *trans* being placed before the numbers indicating the positions of the double bonds to describe the relative positions of the carbon atoms in the main chain; thus VII is 3-*iso*propylhexa-*cis*-2 : *cis*-4-diene.

If a compound has two double bonds, *e.g.*, CH*a*=CH—CH=CH*b*, four geometrical isomers are possible:



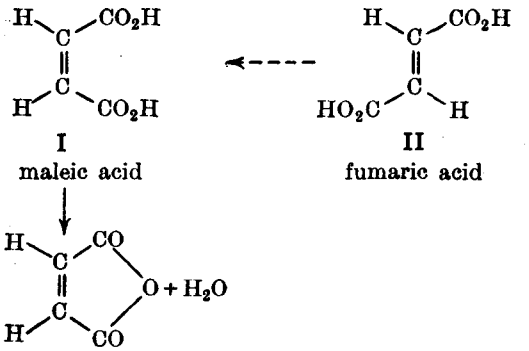
The number of geometrical isomers is 2^n, where n is the number of double bonds; this formula applies only to molecules in which the ends are different. If the ends are identical, *e.g.*, CH*a*=CH—CH=CH*a*, then the number of stereo-

isomers is $2^{n-1} + 2^{p-1}$, where $p = n/2$ when n is even, and $p = \frac{n+1}{2}$ when n is odd (Kuhn *et al.*, 1928).

§5. Determination of the configuration of geometrical isomers. There is no general method for determining the configuration of geometrical isomers. In practice one uses a number of different methods, the method used depending on the nature of the compound in question. The following are methods which may be used mainly for compounds that owe their geometrical isomerism to the presence of a double bond, but several of the methods are special to geometrical isomers possessing a cyclic structure (see also §7).

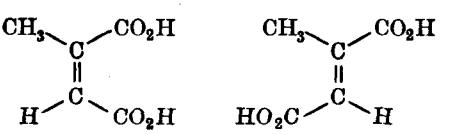
(i) **Method of cyclisation.** Wislicenus was the first to suggest the principle that *intramolecular* reactions are more likely to occur the closer together the reacting groups are in the molecule. This principle appears always to be true for reactions in which *rings* are formed, but does not hold for elimination reactions in which a double (or triple) bond is produced [see, *e.g.*, (xi)].

(*a*) Of the two acids maleic and fumaric, only the former readily forms a cyclic anhydride when heated; the latter does not form an anhydride of its own, but when strongly heated, gives maleic anhydride. Thus I is maleic acid, and II is fumaric acid.

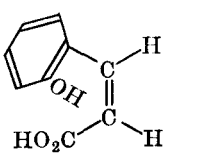


Cyclisation reactions must be performed carefully, since one isomer may be converted into the other during the cyclising process, and so lead to unreliable results. In the above reaction, somewhat vigorous conditions have been used; hence there is the possibility that interconversion of the stereoisomers has occurred. Since maleic acid cyclises readily, and fumaric acid only after prolonged heating, the former is most probably the *cis*-isomer, and the latter the *trans* which forms maleic anhydride *via* the formation of maleic acid (see also §6). The correctness of the conclusion for the configurations of the two acids may be tested by hydrolysing maleic anhydride in the cold; only maleic acid is obtained. Under these mild conditions it is most unlikely that interconversion occurs, and so we may accept I as the configuration of maleic acid.

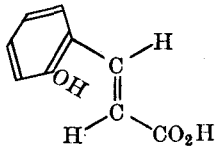
(*b*) Citraconic acid forms a cyclic anhydride readily, whereas the geometrical isomer, mesaconic acid, gives the same anhydride but much less readily. Thus these two acids are:



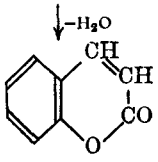
(*c*) There are two *o*-hydroxycinnamic acids, one of which spontaneously forms the lactone, coumarin, whereas the other does not. Thus the former is the *cis*-isomer, coumarinic acid, and the latter the *trans*-isomer, coumaric acid.



coumarinic acid

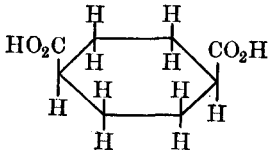


coumaric acid

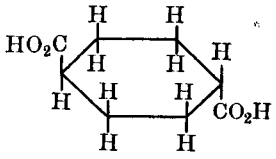


coumarin

(*d*) Two forms of hexahydroterephthalic acid are known, one of which forms a cyclic anhydride, and the other does not. Thus the former is the *cis*-isomer, and the latter the *trans* (see also §§9, 11).

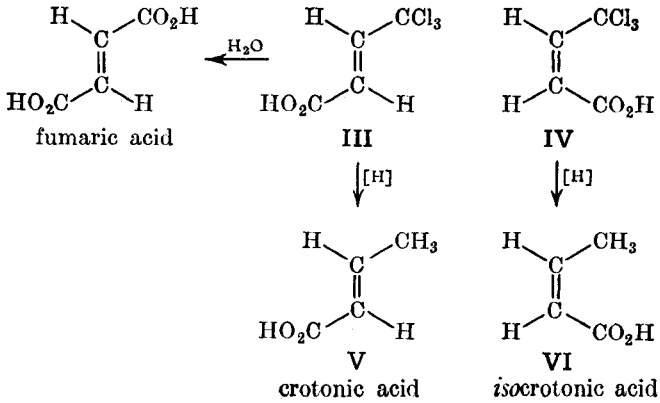


cis-acid



trans-acid

(ii) **Method of conversion into compounds of known configuration.** In a number of cases it is possible to determine the configurations of pairs of geometrical isomers by converting them into compounds the configurations of which are already known. As an example of this type let us consider the two forms of crotonic acid, one of which is known as crotonic acid (m.p. 72°), and the other as *iso*crotonic acid (m.p. 15·5°). Now there are two trichlorocrotonic acids, III and IV, one of which can be hydrolysed to fumaric acid. Therefore this trichlorocrotonic acid must be the *trans*-isomer, III; consequently the other is the *cis*-isomer IV. Both these tri-

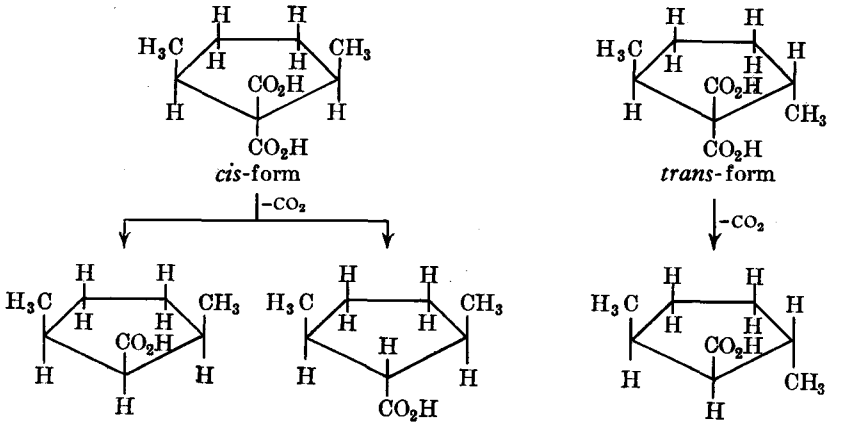


fumaric acid — III — IV

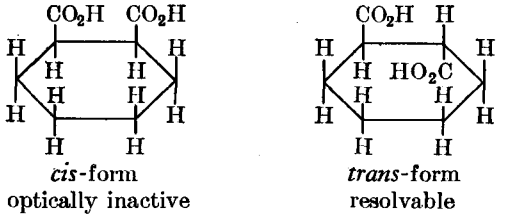
crotonic acid — *iso*crotonic acid

chlorocrotonic acids may be reduced by sodium amalgam and water, or by zinc and acetic acid, to the crotonic acids, III giving crotonic acid, V, and IV giving *iso*crotonic acid, VI. Thus crotonic acid is the *trans*-isomer, and *iso*crotonic the *cis* (von Auwers *et al.*, 1923).

(iii) **Method of conversion into less symmetrical compounds.** Certain pairs of geometrical isomers may be converted into less symmetrical compounds in which the number of geometrical isomers is increased, and by considering the number of products obtained from each original stereoisomer, it is possible to deduce the configurations of the latter. *E.g.*, there are two 2 : 5-dimethyl*cyclo*pentane-1 : 1-dicarboxylic acids, and these, on heating, are decarboxylated to 2 : 5-dimethyl*cyclo*pentane-1-carboxylic acid. Consideration of the following chart shows that the *cis*-form of the original dicarboxylic acid can give rise to *two* stereoisomeric monocarboxylic acids, whereas the *trans*-form can produce only *one* product. Thus the configurations of the dicarboxylic acids are determined (see also §10).



(iv) **Method of optical activity.** In many pairs of geometrical isomers one form may possess the requirements for optical activity (§2. II), whereas the other form may not. In such cases a successful resolution of one form will determine the configuration, *e.g.*, there are two hexahydrophthalic acids; the *cis*-form possesses a plane of symmetry and consequently is optically inactive. The *trans*-form, however, possesses no elements of symmetry, and so should be resolvable; this has actually been resolved (see also §11).



(v) **Method of dipole moments.** The use of dipole moments to assign configurations to geometrical isomers must be used with caution. The method is satisfactory so long as the groups attached to the olefinic carbon atoms have linear moments (see §13. I), *e.g.*, *cis*-1,2-dichloroethylene has a dipole moment of 1·85 D; the value of the dipole moment of the *trans* isomer is zero. When, however, the groups have non-linear moments, then the vector sum in the *trans*-isomer will no longer be zero and the difference

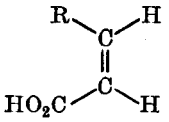
between the dipole moments of the *cis*- and *trans*-isomers may be too small to assign configuration with any confidence, *e.g.*, the dipole moment of diethyl maleate is 2·54 D and that of diethyl fumarate is 2·38 D.

(vi) **X-ray analysis method.** This method of determining the configuration of geometrical isomers is probably the best where it is readily applicable (see also §16. I).

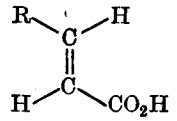
(vii) **Ultraviolet, visible, infra-red, Raman, and NMR spectra methods.** Geometrical isomers may show different spectra, *e.g.*, the intensity of the band in the ultraviolet absorption spectrum depends on the dipole moment (see Vol. I, Ch. XXXI), and this, in turn, depends on the distance between the charges. In the *trans*-form of a *conjugated* molecule, the distance between the ends is greater than that in the *cis*-form. Consequently the intensity of absorption of the *trans*-form is greater than that of the *cis* (see also §15. I). Thus, in cases such as these, it is possible to assign configurations to pairs of geometrical isomers.

NMR spectra (§19a. I) have recently been used to determine configurations of geometrical isomers, *e.g.*, Curtin *et al.* (1958) have used this method to distinguish between the *cis*- and *trans*-isomers of stilbene and azobenzene; Musher *et al.* (1958) have assigned configurations to *cis*- and *trans*-decalin [§11(vii)].

(viii) **Method of surface films.** Long-chain geometrical isomers which contain a terminal group capable of dissolving in a solvent will form surface films, but only the *trans*-form can form a close-packed film, *e.g.*, the long-chain unsaturated fatty acids.

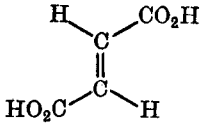


cis-form

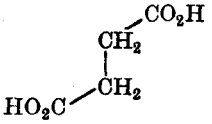


trans-form

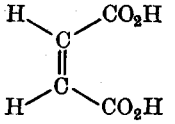
(ix) **Method of formation of solid solutions.** In compounds which owe their property of geometrical isomerism to the presence of an olefinic bond, the shape of the *trans*-form is similar to that of the corresponding saturated compound, whereas that of the *cis*-form is different, *e.g.*, the shapes of fumaric and succinic acids are similar, but the shape of maleic acid is different from that of succinic acid. Now molecules which are approximately



fumaric acid



succinic acid



maleic acid

of the same size and shape tend to form solid solutions. Thus fumaric acid forms a solid solution with succinic acid, whereas maleic acid does not; hence the configurations of maleic and fumaric acids may be determined.

(x) **Methods based on generalisations of physical properties.** Comparison of the physical properties of geometrical isomers of known configurations has led to the following generalisations:

(*a*) The melting point and intensity of absorption of the *cis*-isomer are *lower* than those of the *trans*.

(*b*) The boiling point, solubility, heat of combustion, heat of hydrogenation, density, refractive index, dipole moment and dissociation constant (if the compound is an acid) of the *cis*-isomer are *greater* than those of the *trans*.

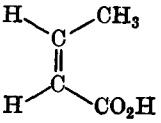
Based on certain of these generalisations is the **Auwers–Skita rule** (1915, 1920), *viz.*, in a pair of *cis-trans* isomers (of alicyclic compounds), the *cis*

has the higher density and refractive index. This rule has been used to elucidate configurations, particularly in terpene chemistry, *e.g.*, the menthones (see §16. VIII), but recently it has been shown that the use of this rule may give misleading results (see §11).

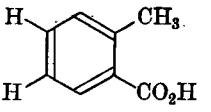
It can be seen from the above physical properties that the *trans*-form is usually the stabler of the two isomers, *i.e.*, the *trans*-isomer is the form with the lower internal energy (*cf.* §2).

Thus, in general, the above physical properties may be used to determine the configurations of unknown geometrical isomers, but the results should always be accepted with reserve, since exceptions are known. Even so, determination of as many as possible of the above physical properties will lead to reliable results, since deviations from the generalisations appear to be manifested in only one or two properties. It should also be noted that where the method of dipole moments can be applied, the results are reliable [*cf.* (v)].

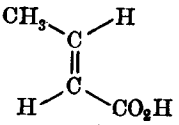
Another method based on generalisations of physical properties is that suggested by Werner. Werner (1904) pointed out that ethylenic *cis-trans* isomers may be compared with the *ortho*- and *para*-isomers in the benzene series, the assumption being made that the melting points of the *cis*- and *ortho*-isomers are lower than those of the corresponding *trans*- and *para*-somers, *e.g.*,



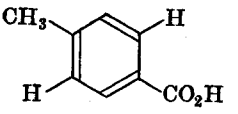
cis-crotonic acid
m.p. 15·5°



o-toluic acid
m.p. 105°

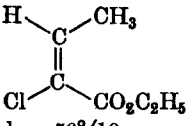


trans-crotonic acid
m.p. 72°

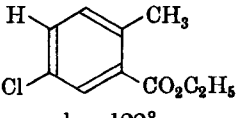


p-toluic acid
m.p. 180°

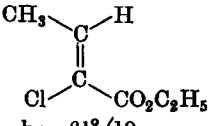
Thus comparison of melting points offers a means of assigning configurations to geometrical isomers. Examination of the above structures shows that, as far as the shape of the molecule is concerned, the benzene ring may be regarded as usurping the function of C=C in the olefinic compound. By making use of this idea, it has been possible to assign configurations to difficult cases of geometrical isomerism, *e.g.*, there are two ethyl α-chlorocrotonates, and by comparing their physical properties with ethyl 5-chloro-*o*- and 3-chloro-*p*-toluates, configurations may be assigned to the chlorocrotonates.



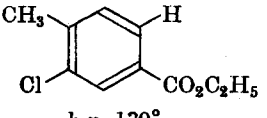
b.p. 56°/10 mm



b.p. 122°



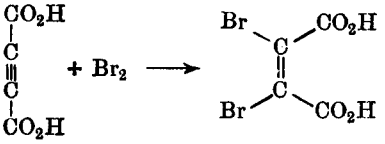
b.p. 61°/10 mm.



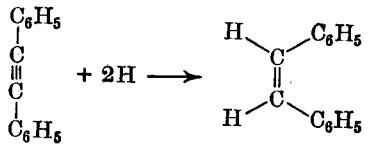
b.p. 130°

(xi) **Method of stereospecific addition and elimination reactions.** This method for determining the configurations of geometrical isomers is based on the assumption that addition reactions to a double or triple bond always occur in a definite manner—either *cis* or *trans*—for a given addendum under given conditions. Similarly, elimination reactions are also assumed to take place in a definite manner.

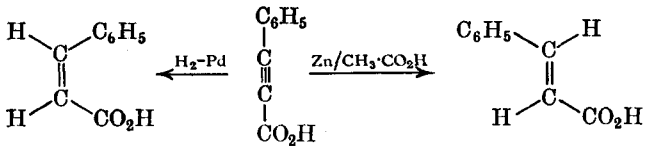
(*a*) **Conversion of acetylenic compounds into ethylenic compounds, and *vice versa*.** This problem was first studied by Wislicenus (1887), who suggested that when one of the acetylenic bonds is broken, the two groups of the addendum should add on in the *cis*-position, *e.g.*, the addition of bromine to acetylenedicarboxylic acid should produce dibromomaleic acid.



In practice, however, a mixture of dibromofumaric and dibromomaleic acids is obtained, with the former predominating. Similarly, halogen acids add on to give mainly halogenofumaric acid. Thus, in these two examples, the suggestion of Wislicenus is incorrect. On the other hand, the reduction of tolan with zinc dust and acetic acid (Rabinovitch *et al.*, 1953) produces *iso*stilbene (the *cis*-compound):



This is a *cis*-addition, but the problem of reduction of a triple bond is complicated by the fact that the results depend on the nature of the compound and the conditions used, *e.g.*, Fischer (1912) found that phenylpropiolic acid on catalytic reduction gave *cis*-cinnamic acid, whereas on reduction with zinc dust and acetic acid, *trans*-cinnamic acid was obtained.

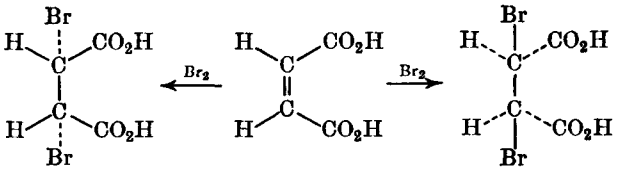


Benkeser *et al.* (1955), on the other hand, have shown that the reduction of acetylenes with lithium in aliphatic amines of low molecular weight produces *trans*-olefins. It appears that, in general, chemical reduction produces the *trans*-olefin, whereas catalytic hydrogenation produces the *cis*-olefin. As a result of a large amount of experimental work, it has been found that addition reactions to a triple bond where the addenda are halogens or halogen acids produce predominantly the *trans*-ethylenic compound, and so, using this generalisation, one can determine the configurations of geometrical isomers when prepared from acetylenic compounds (provided, of course, the addenda are halogen or halogen acid).

Wislicenus also supposed that removal of halogen, halogen acid, etc., from olefinic compounds to produce acetylenic compounds was easier in the *cis*-position than in the *trans*. This again was shown to be incorrect experimentally, and thus the elimination reaction may be used to determine

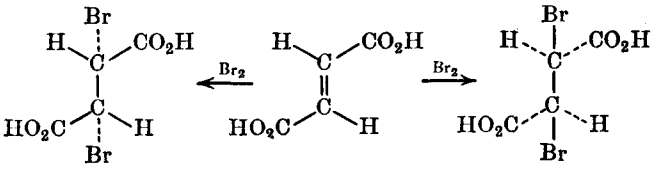
configuration if the assumption is made that *trans*-elimination occurs more readily than *cis* (see also oximes, §2f. VI).

(*b*) **Conversion of ethylenic compounds into ethane derivatives, and *vice versa*.** Just as it was *assumed* that the addition of halogens and halogen acids to a triple bond takes place in the *cis*-position, so the same assumption was made with respect to the double bond. Thus the addition of bromine to maleic acid should give *meso*-α : α'-dibromosuccinic acid. Configurations VII (formed by attack from *behind* the molecule) and VIII



VII VIII

(formed by attack in *front*) are identical, both being the same *meso*-dibromosuccinic acid. Similarly fumaric acid would be expected to give (±)-α : α'-dibromosuccinic acid. IX and X are mirror images, and since they will be



IX X

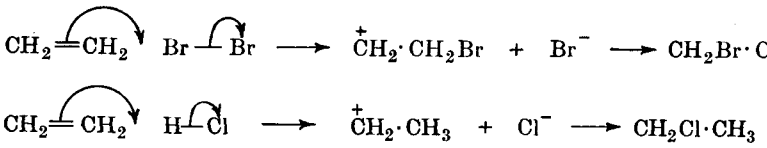
formed in equal amounts (see §7a. II), the racemic modification is produced. Experimental work, however, has shown that the reverse is true, *i.e.*, maleic acid gives mainly (±)-dibromosuccinic acid (IX and X), and fumaric acid gives mainly *meso*dibromosuccinic acid (VII). Thus the addition of bromine must be *trans*. In the same way it has been shown that the addition of halogen acid is also *trans*. Hence, assuming *trans*-addition always occurs with these addenda, the nature of the products indicates the configuration of the ethylenic compound.

The configuration of the product formed by hydroxylation of a double bond depends on the nature of the hydroxylating agent used and on the conditions under which the reaction is carried out. Permanganate and osmium tetroxide apparently always give *cis*-addition, whereas permonosulphuric acid (Caro's acid) and perbenzoic acid give *trans*-addition. On

Reagent	Type of addition	Maleic acid	Fumaric acid
$KMnO_4$	*cis*	*meso*tartaric acid	DL-tartaric acid
OsO_4	*cis*	*meso*tartaric acid	DL-tartaric acid
H_2SO_5	*trans*	DL-tartaric acid	*meso*tartaric acid
$C_6H_5{\cdot}CO{\cdot}O_2H$ . . .	*trans*	DL-tartaric acid	*meso*tartaric acid
H_2O_2—OsO_4 . . .	*cis*	*meso*tartaric acid	DL-tartaric acid
H_2O_2—SeO_2 . . .	*trans*	DL-tartaric acid	*meso*tartaric acid

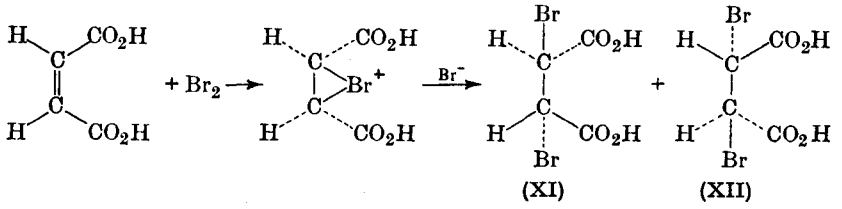
the other hand, hydroxylation with hydrogen peroxide catalysed by osmium tetroxide in *tertiary*-butanol gives *cis*-addition; if the reaction is catalysed by selenium dioxide in *tertiary*-butanol or in acetone, then the addition is *trans* (see also below). The table above shows the products formed by hydroxylation of maleic and fumaric acids.

§5a. Stereochemistry of addition reactions. The mechanisms of the addition of halogen and halogen acids to olefinic double bonds and the hydroxylation of olefinic double bonds have been discussed in Vol. I (Ch. IV). Here we shall discuss the stereochemical aspects of these additions. As we have seen, the *polar* addition of halogen and halogen acid is two-stage and electrophilic; *e.g.*,



It has already been demonstrated above (xi*b*) that experimental results have proved that these additions are almost entirely *trans*. The two-stage mechanism is consistent with *trans*-addition.

In order to account for *trans*-addition, Roberts and Kimball (1937) suggested that the first step is the formation of a cyclic halogenium ion, *e.g.*, with bromine the brominium (bromonium) ion is formed first. If a classical carbonium ion were formed first, then one could expect free rotation about the newly-formed single bond and in this case the stereochemical addition would not be the one observed in practice. Thus for maleic acid the reaction may be formulated as follows:



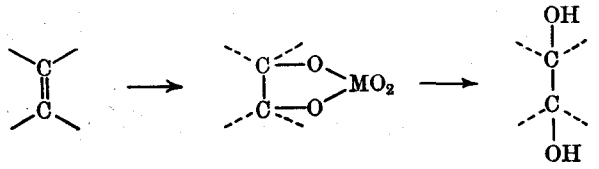
Since the bromide ion can attack " conveniently " only along the C—Br^+ bonding line and on the side remote from the bromine, a Walden inversion occurs at the carbon atom attacked. Since the brominium ion is symmetrical, it can be anticipated that either carbon atom will be attacked equally well, thereby resulting in the formation of (XI) and (XII) in equal amounts, *i.e.*, maleic acid will produce (±)-dibromosuccinic acid. Winstein and Lucas (1939) have demonstrated the existence of this cyclic ion (see §6b. III).

The above mechanism explains *trans*-addition, but, as we have seen, although this predominates, it is not exclusive. The reason for this is not certain, but it is possible that the cyclic ion is not firmly held, *i.e.*, the ring opens to give the classical carbonium ion, and this is followed by rotation about the single C—C bond due to electrostatic repulsion between the carboxyl groups. This would explain the experiments of Michael (1892) that both the maleate ion and fumarate ion add chlorine or bromine to give mainly *meso*-dihalogenosuccinic acid. The configurations of the products indicate that *trans*-addition has occurred with the fumarate ion but *cis*-addition with the maleate ion. Roberts and Kimball, however, have explained these results by assuming that the intermediate maleate brominium ion (*cis*) changes to the fumarate brominium ion (*trans*) due to the powerful repulsions of the negatively charged carboxylate ion groups.

Additions to a triple bond may be assumed to take place by the mechanism proposed for a double bond.

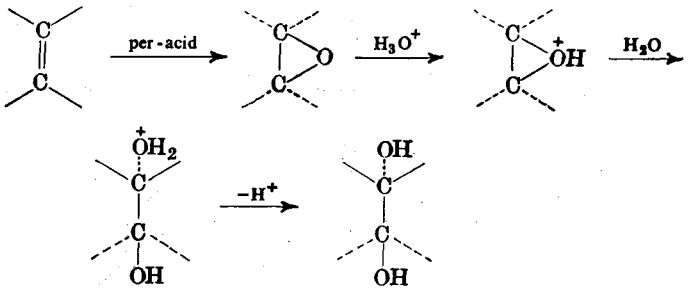
Now let us consider the mechanism of hydroxylation, *i.e.*, the addition of two hydroxyl groups to a double bond. With potassium permanganate

and osmium tetroxide the *cis*-addition is readily explained by assuming the formation of a cyclic organo-metallic intermediate.



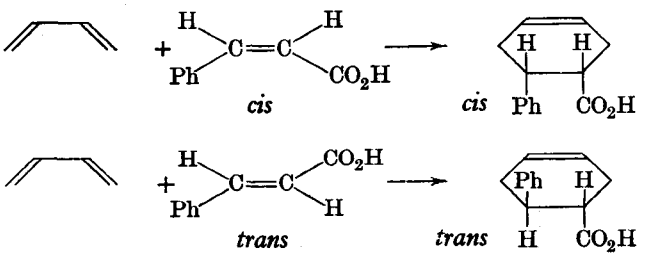
This cyclic intermediate is definitely known in the case of osmium tetroxide (see Vol. I); for potassium permanganate it may be assumed that the permanganate ion, MnO_4^- (or the manganate ion, $MnO_4^{=}$), behaves in a similar manner. This is supported by the work of Wiberg *et al.* (1957), who used potassium permanganate labelled with ^{18}O and showed that *both* glycol oxygen atoms come from the permanganate ion. This also indicates that fission of the cyclic compound occurs between the O and Mn atoms.

With per-acids the hydroxylation results in *trans*-addition. The first product of oxidation is an epoxide (Prileschaiev reaction; see Vol. I). Evidence from kinetic studies on solutions of epoxides under high pressure strongly suggests that acid-catalysed hydrolysis is a bimolecular substitution of the conjugate acid (Whalley *et al.*, 1959). This will result in *trans*-hydroxylation. Thus:



The addition of hydrogen peroxide may result in *cis* or *trans* compounds. Which occurs depends on the conditions of the experiment, *e.g.*, the catalyst (see above). Where *trans*-addition occurs, the mechanism may possibly be through the epoxide, but a free hydroxyl radical mechanism could also result in the *trans*-glycol. *Cis*-addition in the presence of certain oxides probably occurs *via* a cyclic intermediate.

The addition of a dienophile to a diene in the Diels-Alder reaction is stereospecific; *cis*-addition always occurs (see Vol. I). Since it is usually possible to determine the configuration of the cyclic adduct, this offers a means of ascertaining the configuration of the dienophile. *E.g.*, butadiene forms adducts with *cis*- and *trans*-cinnamic acids, and hence determination of the configurations of the stereoisomeric adducts will determine the configurations of the cinnamic acids (see §11); thus:



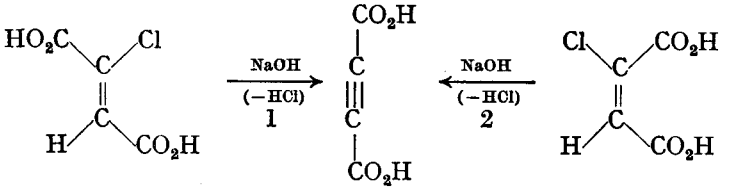
§5b. Stereochemistry of elimination reactions. The mechanisms of elimination in alkyl halides and 'onium salts have been discussed in Vol. I (Ch. V, XIII, XIV). Here we shall deal mainly with the stereochemical aspects of elimination reactions. In olefin-forming eliminations, two mechanisms are possible, E1 and E2, *e.g.*,

E1 $H-CR_2-CR_2-Z \underset{}{\overset{\text{slow}}{\rightleftharpoons}} Z^- + H-CR_2-\overset{+}{C}R_2 \xrightarrow{\text{fast}} H^+ + CR_2=CR_2$

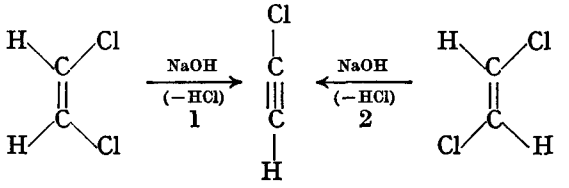
E2 $Y^- + H-CR_2-CR_2-Z \longrightarrow YH + CR_2=CR_2 + Z^-$

Many examples in the literature show that *trans* elimination occurs more readily than *cis*, *e.g.* (also see later):

(*a*) Michael (1895) showed that reaction 1 was about 50 times as fast as 2.

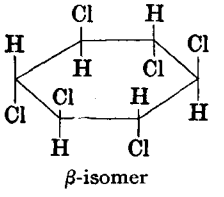


(*b*) Chavanne (1912) showed that reaction 1 was about 20 times as fast as 2.



(*c*) Cristol (1947) showed that the β-isomer of hexachloro*cyclo*hexane underwent base-catalysed elimination with great difficulty, whereas under the same conditions all the other known isomers (four at that time; see also §11) readily underwent second-order elimination to form trichlorobenzenes; the β-isomer is the only one in which *all* the 1,2-HCl pairs are *cis*. Thus in the E2 reaction, the *trans* requirement is necessary (see also below).

According to Hughes and Ingold, bimolecular elimination reactions (E2) take place when the two groups (to be eliminated) are *trans* and the groups

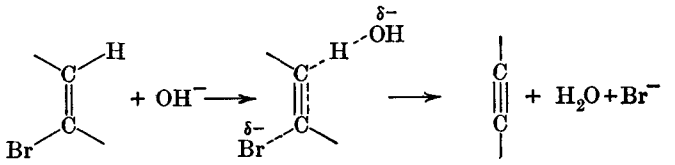


β-isomer

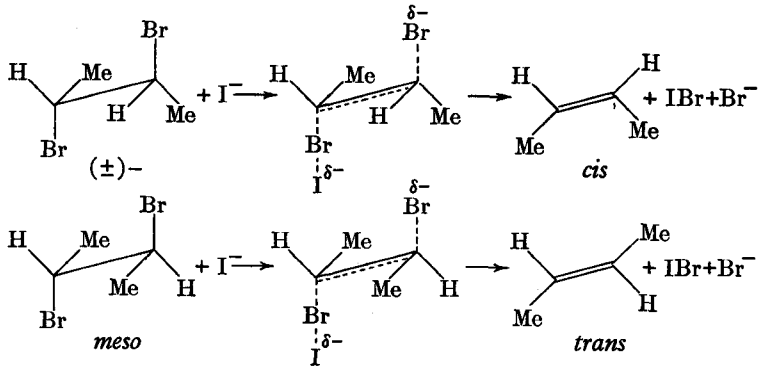
and the two carbon atoms (to which the groups are attached) *all lie in one plane*. In this way the planar transition state will be readily formed. As the proton is being removed from the β-carbon atom by the base, the

"liberated" covalent pair of electrons attacks the α-carbon atom from the rear, thereby forming the double bond with displacement of the halogen atom. This type of sequence is not possible when the β-hydrogen atom is *cis* to the halogen atom.

Before discussing olefin-forming eliminations, let us consider acetylenic-forming eliminations. As already pointed out above, the elimination has been found to occur more readily in the *trans*-isomer than in the *cis*. This may be explained by assuming that the elimination occurs by the E2 mechanism:



Now let us consider eliminations in ethane derivatives to form ethylene derivatives, *e.g.*, the debromination of 2 : 3-dibromobutane by means of potassium iodide in acetone solution. Winstein *et al.* (1939) showed that this reaction is bimolecular (first order in dibromide and first order in iodide ion). Thus, in the transition state, the two carbons (of the CBr groups) and the two bromine atoms will all lie in the same plane and at the same time the two bromine atoms will be in the staggered position. Now 2 : 3-dibromobutane exists in (+)-, (−)- and *meso*-forms, and it has been shown that the (±)-form gives *cis*-butene, whereas the *meso*-form gives *trans*-butene. These eliminations may therefore be written as follows (following Winstein *et al.*, 1939; the iodine atom is probably in the same plane as the other four groups involved in the planar transition state):

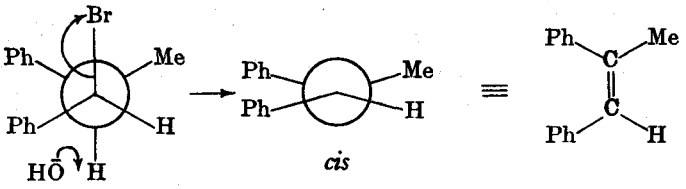


In the (±)-form, as the transition state changes into the ethylene compound, the two methyl groups become eclipsed; in the *meso*-form a methyl group becomes eclipsed with a hydrogen. Thus the energy of activation of the transition state of the (±)-form will be greater than that of the *meso*-form and consequently the latter should be formed more readily, *i.e.*, the *meso*-form should undergo debromination more readily than the (±)-form. Winstein *et al.* (1939) have shown that this is so in practice, the rate of debromination being about twice as fast. These authors also showed that the rate of debromination of *meso*-stilbene dibromide

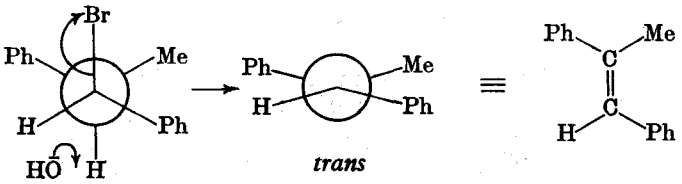
(Ph·CHBr·CHBr·Ph)

is about 100 times as fast as that of the (±)-form.

Cram *et al.* (1952) have shown that the base-catalysed dehydrobromination of the diastereoisomeric 1-bromo-1 : 2-diphenylpropanes (I and II) gives olefins that can only arise by *trans* elimination.



(I)

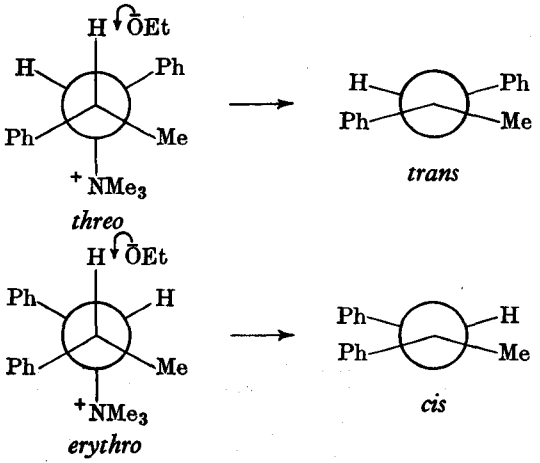


(II)

Cram *et al.* (1956) examined the elimination reaction of the following 'onium ion with base:

$$PhCHMe{\cdot}CHPh{\cdot}NMe_3^+\}I^- \xrightarrow{OEt^-} PhMeC{=}CHPh$$

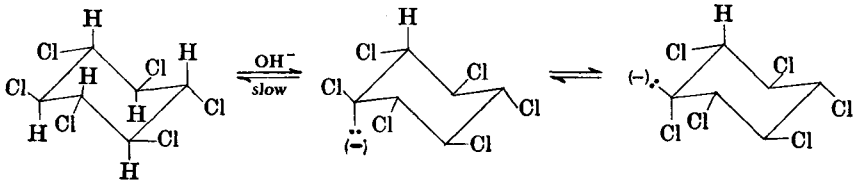
This 'onium ion exists in two forms, *threo* and *erythro*, and the results were that the *threo*-compound gave the *trans*-olefin and the *erythro*-compound



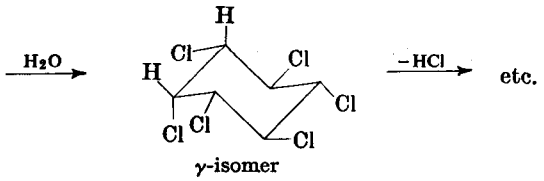
the *cis*-olefin; this is in keeping with *trans* elimination. The rates of elimination, however, were very different, the *threo*-form reacting over 50 times as fast as the *erythro*. In the *cis*-product, the two phenyl groups become eclipsed and hence the energy of activation for this product is greater than that for the *trans*-product, and consequently the latter is formed more readily (see also §12).

An interesting point that now arises is: What is the mechanism when

the two eliminated groups *cannot* assume the *trans*-position? An example of this type is the *β*-isomer of hexachloro*cyclo*hexane. Cristol (1951, 1953) and Hughes, Ingold *et al.* (1953) have proposed that the first step, which is the rate-determining one, is the formation of a *carbanion*:



β-isomer



γ-isomer

It should be noted that even if the chair form of the *β*-isomer given above could change to its other chair form, the " ideal " *trans*-position of 1,2-HCl would still not be achieved; the conformations of all hydrogens and chlorines would be reversed. It is possible, however, when *both* groups to be eliminated are equatorial, that both become axial if the ring is sufficiently flexible. Thus the favourable conformation would be produced, but the elimination would be slowed down since energy must be supplied for this conversion. When the two groups cannot assume the favourable *trans*-position, the normal E2 mechanism will not operate. It appears most likely that the elimination then proceeds *via* the formation of carbanions. It is possible, however, that the elimination might proceed by the E1 mechanism (see *trans*-4-*t*-butyl*cyclo*hexyl tosylate, §12).

§6. Interconversion (stereomutation) of geometrical isomers. The *cis*-isomer, being usually the more labile form, is readily converted into the *trans*-form under suitable physical or chemical conditions. The usual chemical reagents used for stereomutation are halogens and nitrous acid, *e.g.*,

$$\text{maleic acid} \xrightarrow{Br_2;\ I_2} \text{fumaric acid}$$

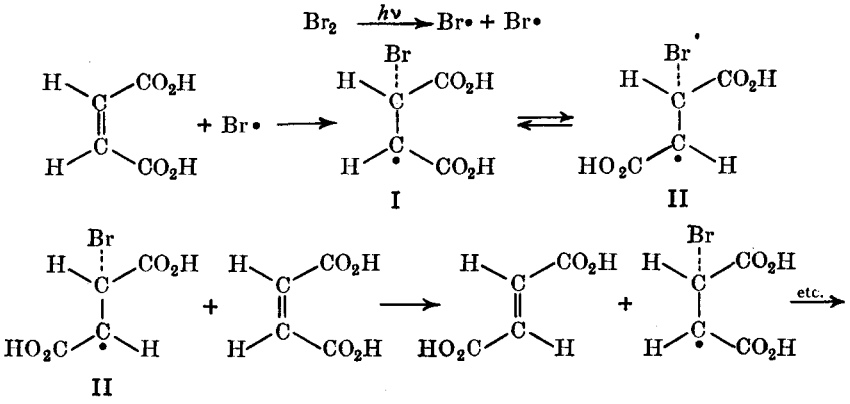
$$\text{oleic acid} \xrightarrow{HNO_2} \text{elaidic acid}$$

Other methods such as distillation or prolonged heating above the melting point also usually convert the *cis*-isomer into the *trans*, but, in general, the result is a mixture of the two forms.

The conversion of the *trans*-isomer into the *cis* may be effected by means of sunlight, but the best method is to use ultraviolet light in the presence of a trace of bromine.

Many theories have been proposed for the interconversion of geometrical isomers, but none is certain. To effect conversion, the double bond must be " dissociated " so as to allow rotation about the single bond (*i.e.*, the *σ*-bond; see §3). Let us consider the conversion of maleic acid into fumaric acid under the influence of light and in the presence of a trace of bromine. One mechanism that has been suggested for this change is a free-radical

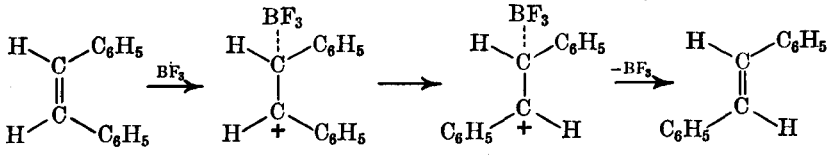
chain reaction, since the conversion does not appear to be effected by bromine in the dark. Thus:



In free radicals I and II, the upper carbon atom is in a state of tetrahedral hybridisation, and the lower one (the free radical part) in a trigonal state (and therefore flat). Owing to the repulsion between the carboxyl groups, configuration I tends to change into configuration II by rotation about the single bond (*cf.* §4. II). If II now reacts with a molecule of maleic acid, the latter is converted into a free radical containing the bromine atom, and II is converted into fumaric acid *if "inversion" occurs on the lower carbon atom*; if no "inversion" occurs, II would form maleic acid again.

Similarly, various other reagents are also believed to act by a free-radical mechanism, *e.g.*, the conversion of *cis*-stilbene into *trans*-stilbene by means of light in the presence of hydrogen bromide. In the absence of light, the conversion takes place very slowly, but in the presence of oxygen or benzoyl peroxide, the conversion is rapid. These reagents are known to generate free radicals; this supports the free-radical mechanism, the reaction being initiated by the formation of free radicals from the hydrogen bromide. Furthermore, if the reaction is carried out in the presence of benzoyl peroxide *and quinol*, the conversion of *cis*- into *trans*-stilbene is extremely slow. This is in keeping with the free-radical mechanism, since it is known that quinol removes free radicals.

Boron trifluoride also catalyses the conversion of *cis*- into *trans*-stilbene. In this case the mechanism is less certain, but a reasonable one is:



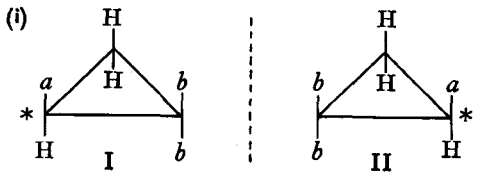
Now let us consider *thermal* interconversion. Kistiakowsky (1935) has shown experimentally that there are at least two mechanisms for thermal *cis-trans* isomerisation of ethylene compounds, and that both are first-order reactions. Experimental results have also shown that one mechanism requires a high and the other a low energy of activation. In the transition state (in both thermal and chemical isomerisations), the two parts of the molecule are perpendicular to each other. To reach this state the double bond, as we have seen, must undergo "dissociation"; this occurs by the decoupling of the π-electrons. The spins of these electrons may remain anti-parallel in the perpendicular (*i.e.*, transition) state. This type of "dis-

sociation " of a double bond requires energy of about 40 kg.cal., and the transition is said to be from a singlet ground state to an upper singlet state. On the other hand, it is also possible for the spins of the π-electrons to be parallel (this state is said to be the triplet state), and the energy required for this " dissociation " is about 25 kg.cal. It has been observed that alkylated ethylenes favour the triplet-state pathway, whereas arylated ethylenes favour the singlet-state pathway (see table in §2).

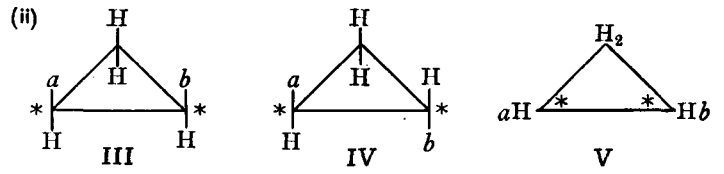
§7. STEREOCHEMISTRY OF CYCLIC COMPOUNDS

Geometrical and optical isomerism may exist in any sized ring. In the following account, the saturated rings are treated as rigid flat structures, and the groups attached to the ring-carbon atoms are regarded as being above or below the plane of the ring (see also, in particular, *cyclo*hexane compounds, §11). Furthermore, the examples described deal only with those cases in which the asymmetric carbon atoms are part of the saturated ring system. In general, the pattern of optical isomerism followed by cyclic compounds is similar to that of the acyclic compounds. The main difference between the two is that, since there is no free rotation about ring-carbon atoms, geometrical isomerism may therefore be manifested as well as optical isomerism. On the other hand, geometrical isomerism may exist without optical isomerism (see §5 for methods of determination of the configuration of geometrical isomers; see also §§9, 10, 11).

§8. *cyclo*Propane types. Molecule I contains one asymmetric carbon atom (*), and is not superimposable on its mirror image molecule II. Thus I and II are enantiomorphs, *i.e.*, a *cyclo*propane derivative containing one

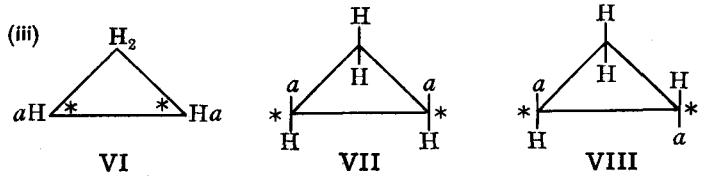


asymmetric carbon atom can exist in two optically active forms (and one racemic modification; *cf.* §7a. II). Molecule III contains two different asymmetric carbon atoms, and since it has no elements of symmetry (§6. II), it is not superimposable on its mirror image molecule. Thus III can exist in two optically active forms (and one racemic modification). Structure III,

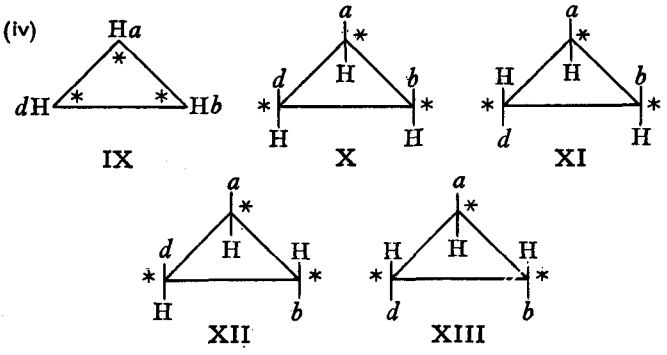


however, is capable of exhibiting geometrical isomerism, the two geometrical isomers being III and IV. Now IV also contains two different asymmetric carbon atoms, and these are not disposed towards each other as in III. Since IV possesses no elements of symmetry, it can also exist in two optically active forms which are different from those of III. Thus V, which may be regarded as the non-committal way of writing the configurations III and IV, is similar, as far as *optical isomerism* is concerned, to the acyclic molecule C*abd*·C*abe*, *i.e.*, there are four optically active forms in all (two pairs of enantiomorphs). In general, any monocyclic system can exist in 2^n

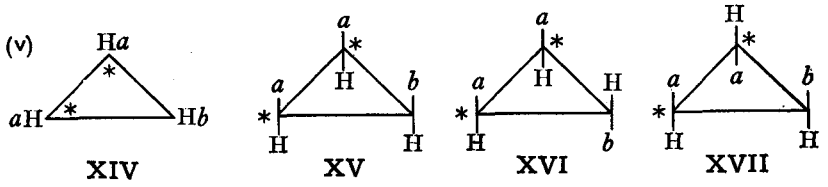
optically active forms, where n is the number of different asymmetric ring-carbon atoms (*cf.* §7c. II). Molecule VI contains two similar asymmetric



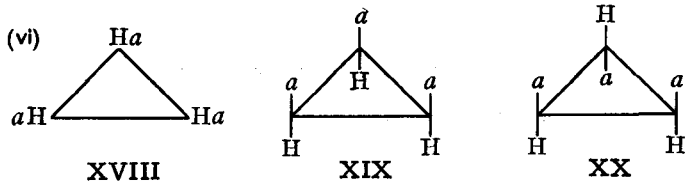
carbon atoms, and can exist as geometrical isomers VII and VIII. VII has a (vertical) plane of symmetry and therefore represents a *meso*-form. VIII, however, possesses no elements of symmetry and can therefore exist in two optically active forms (and one racemic modification). IX contains



three different asymmetric carbon atoms and can therefore exist in $2^3 = 8$ optically active forms (four pairs of enantiomorphs). Each pair of enantiomorphs is derived from the *four* geometrical isomers X–XIII. Inspection of these configurations shows that all of them possess no elements of symmetry. XIV contains two similar asymmetric carbon atoms, and the third



carbon atom is pseudo-asymmetric (*cf.* §7d. II). Three geometrical isomers, XV–XVII, are possible; XV and XVI each possess a (vertical) plane of symmetry, and therefore each represents a *meso*-form. XVII, however, possesses no elements of symmetry and so can exist in two optically active

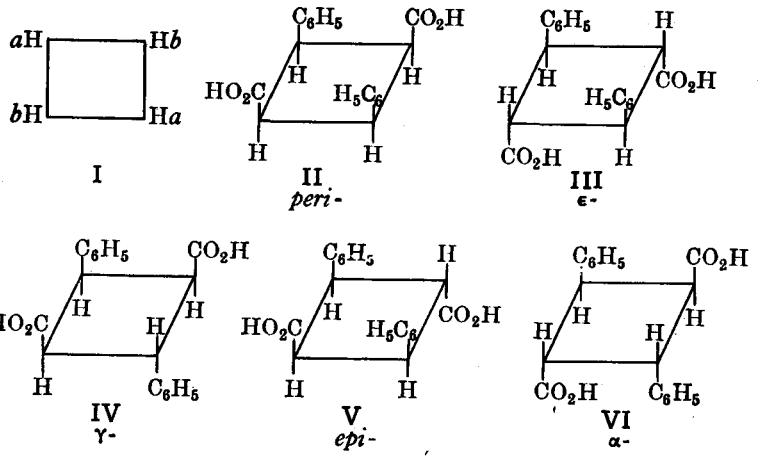


forms (and one racemic modification). XVIII contains three similar asymmetric carbon atoms which are all pseudo-asymmetric. Two geometrical isomers are possible, XIX and XX, both of which possess at least one (vertical) plane of symmetry, and therefore represent *meso*-forms.

In the above account, the stereochemistry of the *cyclo*propane ring has been dealt with from the theoretical point of view, and thus most of the ideas connected with the stereochemistry of monocyclic systems have been described. In the following sections more emphasis is laid on specific examples, and any further points that arise are dealt with in the appropriate section.

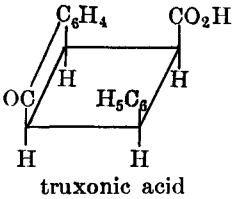
§9. *cyclo*Butane types. Two important examples of the *cyclo*butane type are truxillic and truxinic acids; truxillic acid is 2 : 4-diphenyl*cyclo*butane-1 : 3-dicarboxylic acid, and truxinic acid is 3 : 4-diphenyl*cyclo*butane-1 : 2-dicarboxylic acid. *cis*-Cinnamic acid (allocinnamic acid), on irradiation with light, forms mainly *β*-truxinic acid and *trans*-cinnamic acid, together with some of the dimer of the latter, *α*-truxillic acid (de Jong, 1929). Bernstein *et al.* (1943) found that irradiation of commercial *trans*-cinnamic acid gave only *β*-truxinic acid. When *trans*-cinnamic acid was slowly recrystallised from aqueous ethanol, dried, and then irradiated, only *α*-truxillic acid was obtained. Truxillic and truxinic acids have been isolated from natural sources.

Truxillic acid. This acid can exist theoretically in five stereoisomeric forms, all of which are known (the acid is of the type I). All five are *meso*-forms, II–V having planes of symmetry, and VI a centre of symmetry. The configurations of these stereoisomers have been assigned as follows. When *one* of the carboxyl groups is converted into the anilido-group, $\cdot CONH\cdot C_6H_5$, *two* of the five forms give optically active compounds, each giving a pair of enantiomorphs. Now only the stereoisomers with the two



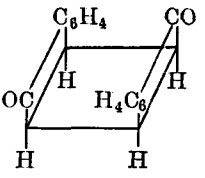
phenyl groups in the *trans*-position can produce asymmetric molecules under these conditions; the remaining forms will each have a (vertical) plane of symmetry. Thus only IV and VI satisfy the necessary conditions. One of these is known as the *α*-acid (m.p. 274°) and the other the *γ*-acid (m.p. 288°). This then raises the problem: Which is which? This is readily answered by the fact that of the anilido-derivatives of these two acids, only one can be dehydrated to a cyclic *N*-phenyl imide, $—CO—N(C_6H_5)—CO—$. This reaction can be expected to take place only when the two carboxyl groups are in the *cis*-position (see §5. i). Therefore IV is *γ*-truxillic acid, and VI is *α*-truxillic acid (since the acid with the melting point 288° has been called the *γ*-acid). By considering the ease of formation of the cyclic anhydride, the configurations of the remaining three stereoisomers may be determined. Two form anhydrides readily, and therefore one of these acids

must be II and the other III. The third acid does not form its own anhydride, but gives a mixture of the anhydrides produced by II and III. Thus the third acid, *epi*-truxillic acid, is V. The final problem is to decide which of the two, II and III, is *peri*-truxillic acid, and which is ε-truxillic acid. *peri*-Truxillic acid, under the influence of aluminium chloride, undergoes an internal Friedel–Crafts reaction to form a truxonic acid, VII, and a truxone, VIII. This is only possible when the phenyl and carboxyl groups are in the *cis*-position. Thus II is *peri*-truxillic acid, and therefore III is ε-truxillic acid.



truxonic acid

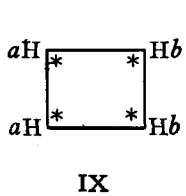
VII



truxone

VIII

Truxinic acid. This acid can exist theoretically in six geometrical isomeric forms, four of which are resolvable; thus ten forms in all are possible theoretically. Truxinic acid is of the type IX, and the six geometrical isomers possible are X–XV. X and XI are *meso*-forms (each has a plane of symmetry); XII–XV are resolvable (theoretically), since all possess no elements of symmetry. The configurations of these stereoisomers have been determined by methods similar to those used for the truxillic acids; it appears, however, that only four of these six forms are known with certainty, *viz.*, β, δ, ζ and *neo*.



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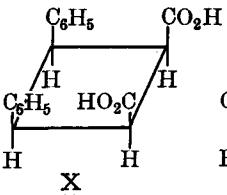
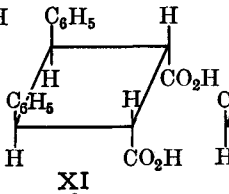
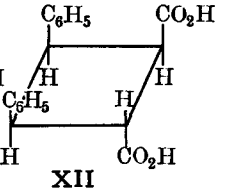


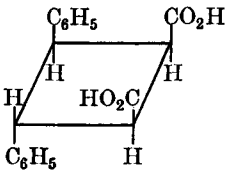
X
ω-



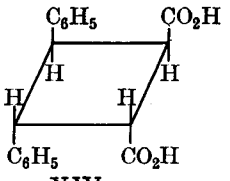
XI
β-



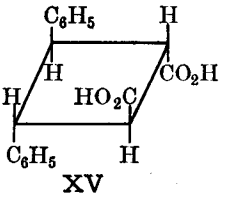
XII
neo-



XIII
ζ-



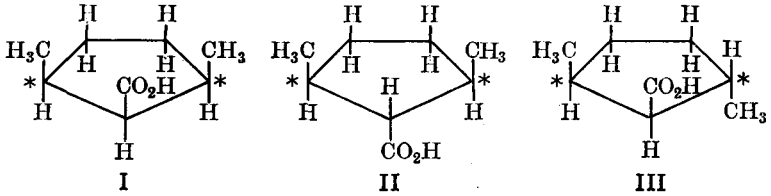
XIV
μ-



XV
δ-

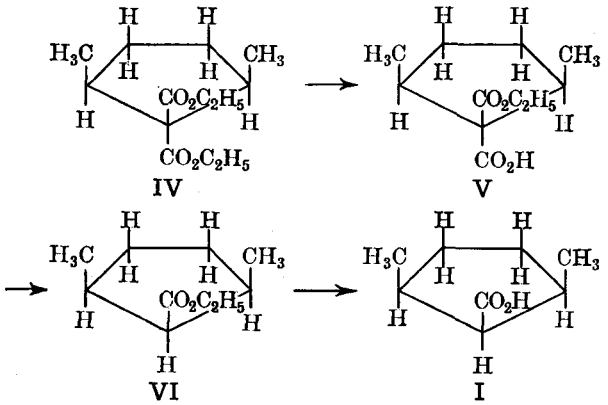
§10. *cyclo*Pentane types. A number of examples involving the stereochemistry of the five-membered ring occur in natural products, *e.g.*, camphoric acid (§23a. VIII), furanose sugars (§7b. VII). In this section we shall discuss the case of 2 : 5-dimethyl*cyclo*pentane-1 : 1-dicarboxylic acid. This acid can exist in two geometrical isomeric forms, which may be differentiated by decarboxylation, the *cis*-isomer giving two monocarboxylic acids, I and II, and the *trans*-isomer one monocarboxylic acid, III (see §5. iii). All three acids contain two similar asymmetric carbon atoms and one pseudo-asymmetric carbon atom. Both I and II possess a (vertical)

plane of symmetry, and are therefore *meso*-forms; III possesses no elements of symmetry, and can therefore exist in two optically active forms (and one racemic modification). All the possible forms are known, and I and II



I II III

have been differentiated as follows. The diethyl ester of the *cis*-dicarboxylic acid, IV, can be partially hydrolysed to the monoethyl ester, which most probably has the configuration V. This is based on the assumption that the carbethoxyl group on the same side as the two methyl groups is far more resistant to attack than the other carbethoxyl group because of the steric effect (see Vol. I). Decarboxylation of V gives VI, and this, on hydrolysis, gives I. Thus the configuration of I (and therefore also of II) is determined.



IV V VI I

The above treatment of the *cyclo*pentane derivatives has been based on the assumption that the ring is planar. This classical treatment leads to agreement between prediction and the number of stereoisomers actually obtained (see *cyclo*hexane, §11, for a further discussion of this problem). It is now known that the *cyclo*pentane ring is not planar; the puckering, however, is very small. The non-planarity of this ring has been shown from entropy determinations (Aston *et al.*, 1941), spectroscopic studies (Miller *et al.*, 1950) and from a study of the polarisabilities of C—$C_{aliphatic}$ and C—H bonds (Le Fèvre *et al.*, 1956).

§11. *cyclo*Hexane types. The stereochemistry of *cyclo*hexane and its derivatives presents a detailed example of the principles of conformational analysis (§4a. II). On the basis of the tetrahedral theory, two forms are possible for *cyclo*hexane, neither of which is planar. These two forms, known as **boat** and **chair conformations** (Fig. 5), were first proposed by Sachse (1890; see Vol. I, Ch. XIX), who also pointed out that both are strainless. Hassel *et al.* (1943) showed by means of electron diffraction studies that at room temperature most of the molecules existed mainly in the chair conformation. Pitzer (1945) then showed by calculation that the energy difference between the two forms is about 5·6 kg.cal./mole (the

boat form having the higher energy content; see also below). This value, however, is too small for stability, and consequently neither conformation retains its identity, each being readily converted into the other.

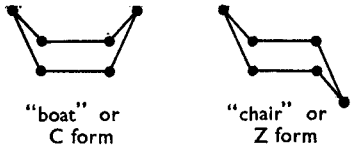
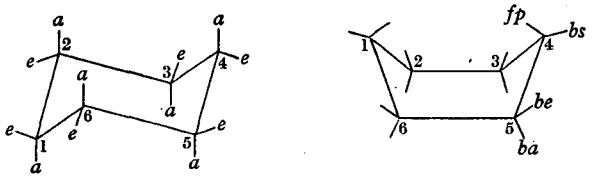


FIG. 4.5.

Although these two forms are free from " angle strain ", forces due to steric repulsion (*i.e.*, repulsive forces between non-bonded atoms) are acting, and it is because of their different total effects that the two conformations differ in energy content. A simple method of calculating this energy difference has been introduced by Turner (1952). Fig. 6 (*a*) and 6 (*b*) represent the chair and boat conformations and the directions of the C—H bonds. In the chair conformation, all the C—H bonds on adjacent carbons are



(*a*) chair form (*b*) boat form

FIG. 4.6.

in the skew position (*i.e.*, the arrangement is skew as in the skew form of *n*-butane, §4. II). On the other hand, in the boat conformation there are four skew interactions (1 : 2, 3 : 4, 4 : 5 and 6 : 1) and two eclipsed interactions (2 : 3 and 5 : 6). According to Pitzer (1940), skew interaction of the hydrogens in *n*-butane is 0·8 kg.cal., and an eclipsed interaction is 3·6 kg.cal. Thus the steric strain in the chair form is $6 \times 0{\cdot}8 = 4{\cdot}8$ kg.cal., and in the boat form $4 \times 0{\cdot}8 + 2 \times 3{\cdot}6 = 10{\cdot}4$ kg.cal. Thus the boat form has the greater energy content, and the amount (according to the above method of calculation) is 5·6 kg.cal. There is, however, a further interaction in the boat form, *viz.* the interaction of the two flagpole (*fp*) hydrogens (at positions 1 and 4). These are closer together than any other two hydrogens (see table below) and so produce an additional steric repulsion. The actual value of this interaction is not certain, but it is believed to be about the same as that of two eclipsed hydrogens. Thus the energy content of the boat form is $10{\cdot}4 + 3{\cdot}6 = 14$ kg.cal., and hence the boat form contains $14 - 4{\cdot}8 = 9{\cdot}2$ kg.cal. more than the chair form.

Johnson *et al.* (1960), from measurements of heat of combustion and other measured quantities, have found that the energy difference between the boat and chair forms of *cyclo*hexane is $5{\cdot}3 \pm 0{\cdot}3$ kg.cal./mole (at 25°; vapour phase). This value has been confirmed by the work of Allinger *et al.* (1960); their value is $5{\cdot}9 \pm 0{\cdot}6$ kg.cal./mole.

Inspection of Fig. 6 (*a*) shows that the twelve hydrogen atoms in the chair conformation are not equivalent; there are two sets of six. In one of these sets the six C—H bonds are parallel to the threefold axis of symmetry of the molecule; these are the **axial** (*a*) **bonds** (they have also been named *ε*- or *polar* bonds). In the other set the six C—H bonds make an angle of 109° 28′ with the axis of the ring (or $\pm$19° 28′ with the horizontal plane of the ring); these are the **equatorial** (*e*) **bonds** (they have also been named

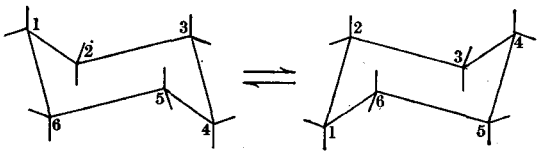
κ-bonds). On the other hand, in Fig. 6 (*b*) it can be seen that the "end" of the boat is different stereochemically from the chair conformation; the various C—H bonds have been named: **flag-pole** (*fp*), **bowsprit**(*bs*), **boat-equatorial** (*be*), and **boat-axial** (*ba*).

Angyal and Mills (1952) have calculated the distances between the various hydrogen atoms (and carbon atoms) in both the chair and boat conformations.

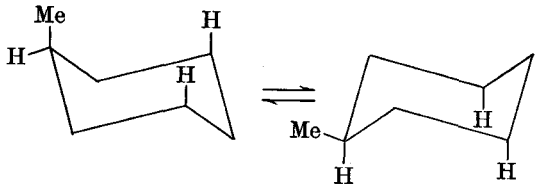
Conformation	*Position*	H—H (A)
Chair	1*e* : 2*e*	2·49
(Fig. 6*a*)	1*e* : 2*a*	2·49
	1*a* : 2*a*	3·06
	1*a* : 3*a*	2·51
Boat	2*a* : 3*a*	2·27
(Fig. 6*b*)	2*e* : 3*e*	2·27
	1*fp* : 4*fp*	1·83

It appears that the boat conformation occurs in relatively few cases, and so in the following account we shall only study the problem of the chair conformation. Inspection of the above table shows that a 1 : 2-interaction for two adjacent equatorial hydrogens or for an equatorial and adjacent axial hydrogen is about the same as for a 1 : 3-interaction for two *meta* axial hydrogens. Furthermore, a study of accurate scale models has shown that with any axial substituent (which is necessarily larger than hydrogen), the 1 : 3-interactions are larger than the 1 : 2-interactions when the same substituent is equatorial. Using these principles, we can now proceed to study the conformations of *cyclo*hexane derivatives.

Because of the flexibility of the chair conformation, one chair form is readily converted into the other chair form, and in doing so all *a*- and *e*-bonds in the first now become *e*- and *a*-bonds, respectively, in the second.



Both forms are identical and so cannot be distinguished. If, however, one hydrogen is replaced by some other atom or group, the two forms are no longer identical, *e.g.*, methyl*cyclo*hexane. In the *a*-methyl conformation



a-methyl *e*-methyl

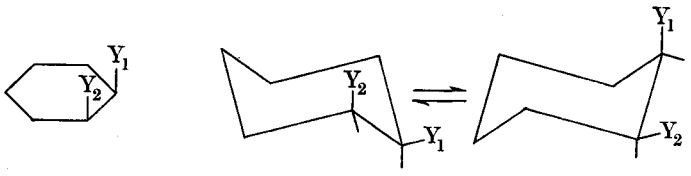
there are 1 : 3-interactions acting, whereas in the *e*-methyl conformation these interactions are absent; instead, the *weaker* 1 : 2-interactions are acting. Thus the energy content of axial conformation is greater than that of the equatorial, and consequently the latter will be the preferred form. Hassel (1947) has shown experimentally from electron-diffraction studies that the *e*-methyl conformation predominates in methyl*cyclo*hexane. Hassel *et al.* (1950) have also shown that in chlorocyclohexane the *e*-form also predominates and that very little of the *a*-form is present.

The nature of the intermediate in the transformation of one chair form into the other is not certain. According to Johnson *et al.* (1961), the boat form of *cyclo*hexane is twisted, and Jensen *et al.* (1962) believe that the transition state (of the intermediate) is the structure approximately halfway between the chair and twisted boat forms.

Now let us discuss the conformations of disubstituted *cyclo*hexanes. Here we have a number of factors to consider: position isomerism, stereoisomerism (geometrical and optical), the relative sizes of the two substituents, and the nature of the substituents.

(i) 1 : 2-Compounds

Classical formula *Conformations*

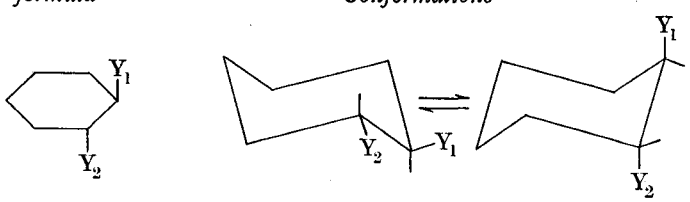


cis-1:2 1*e*:2*a* 1*a*:2*e*

It should be noted that in these *cis*-compounds one substituent must be axial and the other equatorial. If the substituents differ in size, the 1 : 3-interactions will be most powerful when the larger group is axial. Thus the conformation with the lower energy will be the one in which the larger group is equatorial, *i.e.*, this is the preferred form. An example of this type is *cis*-2-methyl*cyclo*hexanol; the methyl group is larger than the hydroxyl, and so the preferred form can be expected to be 1*a*-hydroxyl : 2*e*-methyl. This has been shown to be so in practice. In general, the greater the difference in size between the two substituents, the greater will be the predominance of the form with the larger group in the equatorial conformation.

The classical formula of the *cis*-compound when the two substituents are identical has a plane of symmetry and is therefore not resolvable. On the other hand, the two conformations are mirror images but not superimposable and hence, in theory, are resolvable. Such compounds, however, have never yet been resolved. The reason for this is that the two forms are separated by such a low energy barrier that they are readily interconvertible.

Classical formula *Conformations*



trans-1:2 1*e*:2*e* 1*a*:2*a*

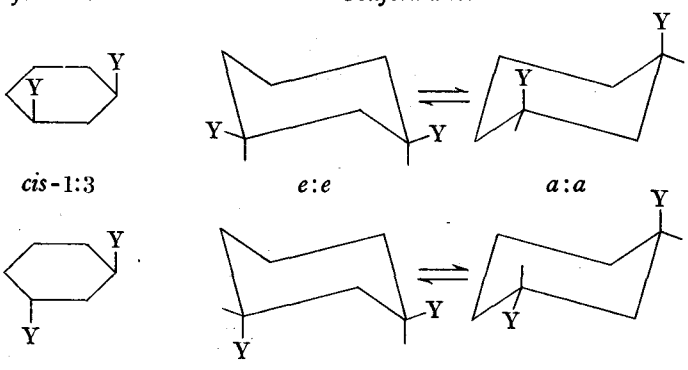
Whether Y_1 and Y_2 are identical or not, the two conformations are different, and because of the 1 : 3-interactions the *e* : *e*-form will be the preferred form. Furthermore, this form will be more stable than the *cis*-isomer (*a* : *e*-form). An example that illustrates this is 2-methyl*cyclo*hexanol. The *trans*-form has been shown to be more stable than the *cis*; the latter is readily converted into the former when heated with sodium, and also the reduction of 2-methyl*cyclo*hexanone (with sodium and ethanol) produces the *trans*-alcohol.

Both the classical formula and the *e* : *e*- (and *a* : *a*) conformation of the

trans-1 : 2-compound (whether Y_1 and Y_2 are identical or not) are not superimposable on their mirror images and hence should be optically active. This has been found to be so in practice.

(ii) **1 : 3-Compounds**

Classical formula *Conformations*



cis-1:3 *e*:*e* *a*:*a*

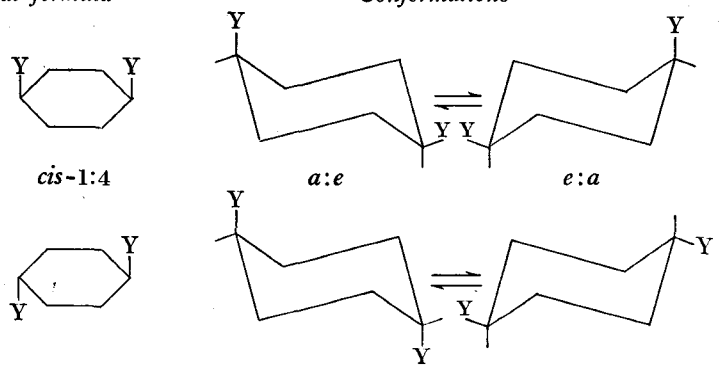
trans-1:3 *a*:*e* *e*:*a*

The two *trans*-conformations are identical when the two Y groups are identical. The *cis*-*e* : *e*-form will be more stable than the *cis*-*a* : *a*, and will also be more stable than the *trans*-*e* : *a*-conformation, *e.g.*, the most stable conformation of 1 : 3-dimethyl*cyclo*hexane has been shown to be the *cis*-1 : 3-*e* : *e*-form. It should be noted that this situation is the reverse of that of the 1 : 2-dimethyl*cyclo*hexanes.

The Auwers-Skita rule (§5(x)*b*) has been shown to break down when applied to 1 : 3-disubstituted *cyclo*hexanes: the reverse holds good. Allinger (1954) modified the rule for *cyclo*hexanes as follows: The isomer which has the higher boiling point, refractive index and density is the one with the less stable configuration. Thus, according to this rule, the *trans*-1 : 3-disubstituted *cyclo*hexanes have the higher physical constants (the *trans*-form has more axial substituents than the more stable *cis*-form); *e.g.*, Macbeth *et al.* (1954) have shown that the physical constants of (±)-*trans*-3-methyl*cyclo*hexylamine are higher than those of its *cis*-isomer.

(iii) **1 : 4-Compounds**

Classical formula *Conformations*



cis-1:4 *a*:*e* *e*:*a*

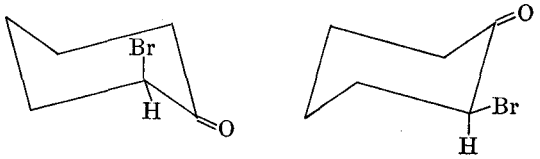
trans-1:4 *a*:*a* *e*:*e*

The two *cis*-conformations are identical when the Y groups are identical. Also, the *trans*-*e* : *e*-form will be more stable than the *cis*-*a* : *e*-form.

The arguments used for the disubstituted *cyclo*hexanes can also be applied to the higher substituted *cyclo*hexanes. As the result of a large amount of work, the following generalisations may be made:

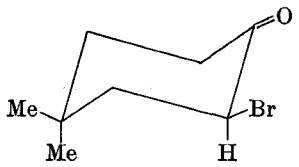
(i) In *cyclo*hexane systems, mono-, di-, tri- and poly-substituted derivatives always tend to take up the chair conformation whenever possible.

(ii) The chair conformation with the maximum number of equatorial substituents will be the preferred conformation. This generalisation, however, is only satisfactory when the internal forces due to dipole interactions or hydrogen bonding are absent. When these are present, it is necessary to determine which forces predominate before a conformation can be assigned to the molecule. As an illustration of this problem, we shall consider 2-bromo*cyclo*hexanone; the two possible chair forms are:



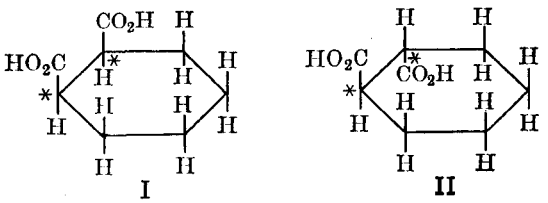
a-Br *e*-Br

On the basis that a substituent preferably takes up an equatorial conformation, it would therefore be expected that the conformation 2*e*-bromo*cyclo*hexanone would be favoured. Infra-red studies, however, have shown that the *a*-bromo conformation predominates. This has been explained as follows. The C—Br and C=O bonds are both strongly polar, and when the bromine is equatorial the dipolar repulsion is a maximum, and a minimum when the bromine is axial. Since the axial form predominates, this equatorial dipolar repulsion must therefore be larger than the 1 : 3-interactions. When, however, other substituents are present, the 1 : 3-interactions may become so large as to outweigh the dipolar effect and the bromine would now be equatorial. Such is the case with 2-bromo-4 : 4-dimethyl*cyclo*hexanone (see also §12).



(iii) The energy barriers between the various conformations are too small to prevent interconversion (but see §12). Up to the present time, the number of geometrical (and optical) isomers obtained from a given *cyclo*hexane derivative is in agreement with the number that can be expected from a planar ring with the substituents lying above and below the plane of the ring. We shall now, therefore, discuss the stereochemistry of some *cyclo*hexane derivatives from the classical point of view.

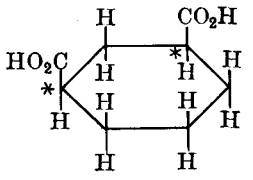
(i) *Hexahydrophthalic acids* (*cyclo*hexane-1 : 2-dicarboxylic acids). Two geometrical isomers are theoretically possible, the *cis*, I, and the *trans*, II.



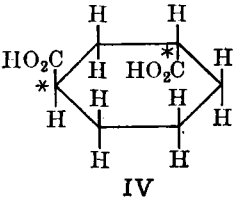
I II

Molecule I has a plane of symmetry, and therefore represents the *meso*-form; II has no elements of symmetry, and can therefore exist in two optically active forms (and one racemic modification). All of these possible forms are known, and it has been found that the *cis*-compound, I, forms a cyclic anhydride readily, whereas the *trans*-compound, II, forms a cyclic anhydride with difficulty (*cf.* §5. i).

(ii) *Hexahydroisophthalic acids* (*cyclo*hexane-1 : 3-dicarboxylic acids). Two geometrical isomers are possible; the *cis*-form, III, has a plane of symmetry, and therefore represents the *meso*-form; IV has no elements of symmetry, and can therefore exist in two optically active forms (and one racemic



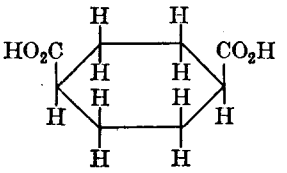
III



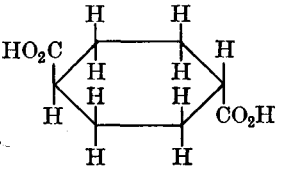
IV

modification). All of these forms are known; the *cis*-isomer forms a cyclic anhydride, whereas the *trans*-isomer does not.

(iii) *Hexahydroterephthalic acids* (*cyclo*hexane-1 : 4-dicarboxylic acids). Two geometrical isomers are possible; the *cis*-form, V, has a plane of symmetry, and the *trans*-form, VI, a centre of symmetry. Hence neither is



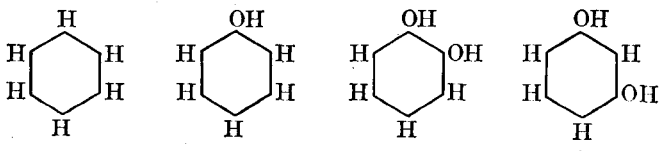
V



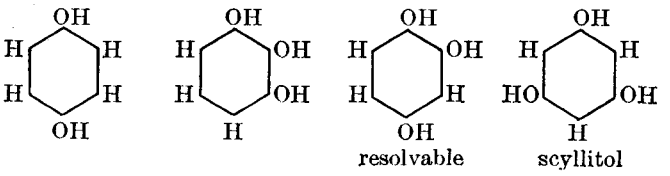
VI

optically active. They may be distinguished by the fact that the *cis*-isomer forms a cyclic anhydride, whereas the *trans*-isomer does not.

(iv) *Inositol* (hexahydroxy*cyclo*hexane). There are eight geometrical isomers possible theoretically, and only *one* of these is not superimposable on its mirror image molecule; thus there are nine forms in all (and also one racemic modification). If we imagine that we are looking down at the molecule, and insert the groups which appear *above* the plane of the ring, then the eight geometrical isomers may be represented as follows:



meso-inositol



resolvable scyllitol

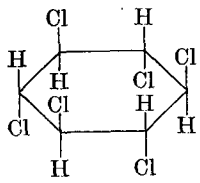
Examination of these configurations shows that all except one—the one labelled resolvable—have at least one plane of symmetry, and so are all

meso-forms. All the *meso*-forms and both of the optically active forms are known; of these *meso*-inositol, scyllitol and (+)- and (−)-inositol occur naturally.

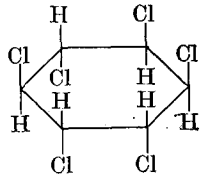
(v) *Benzene hexachloride* (hexachloro*cyclo*hexane). Here again eight geometrical isomers are possible theoretically; seven are known, α, β, γ, δ, ε, η, θ; the γ-isomer is a powerful insecticide (see Vol. I). All have been shown to exist in the chair form, and the conformations that have been assigned are:

α-, *aaeeee*; β-, *eeeeee*; γ-, *aaaeee*; δ-, *aeeeee*; ε-, *aeeaee*.

Of these forms, it is the β- which loses hydrogen chloride with the greatest difficulty (see §5b). All of the other stereoisomers possess at least one



β−



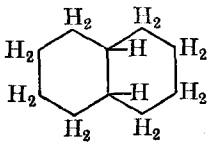
α−

pair of chlorine atoms *cis* to each other (thus having H and Cl *trans*). Cristol (1949) has also identified the α-isomer as the (±)-form.

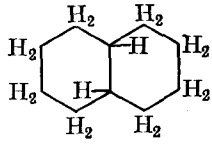
(vi) So far, we have discussed the stereochemistry of the *cyclo*hexane ring. The same types of stereoisomerism are also exhibited by various sized heterocyclic systems, *e.g.*, dimethyldiketopiperazine (§6. II), furanose (§7b. VII) and pyranose (§7a. VII) sugars.

(vii) *Decalins and decalols.* As we have seen, the boat and chair forms of *cyclo*hexane are readily interconvertible, and the result is that *cyclo*hexane behaves as if it were planar. Mohr (1918), however, elaborated Sachse's theory, and predicted that the fusion of two *cyclo*hexane rings, *e.g.*, as in decalin, should produce the *cis*- and *trans*-forms which would be sufficiently stable to retain their identities. This prediction has now been confirmed experimentally.

A non-committal way of writing the two geometrical isomers of decalin is given by formulæ VII and VIII. On the other hand, several conventions

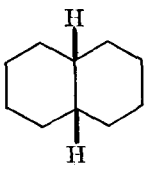


VII
cis-decalin

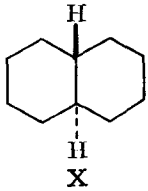


VIII
trans-decalin

have been introduced to represent these isomers. One convention uses *full* lines to represent groups *above* the plane of the molecule, and *broken* lines to represent those *below* the plane (*cf.* §5. xi); thus *cis*-decalin will be IX

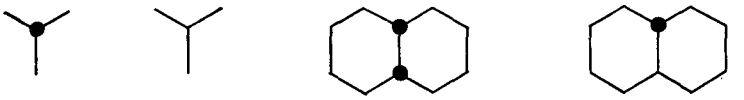


IX
cis-



X
trans-

and *trans*-decalin X. This convention appears to be the one most widely used (see, *e.g.*, Steroids, Ch. XI), but there is another, introduced by Linstead (1937), which is favoured by many. According to this convention, a hydrogen atom is represented as being above the plane of the ring when drawn as in XI, and below the plane when drawn as in XII; thus *cis*-decalin will be XIII, and *trans*-decalin XIV.



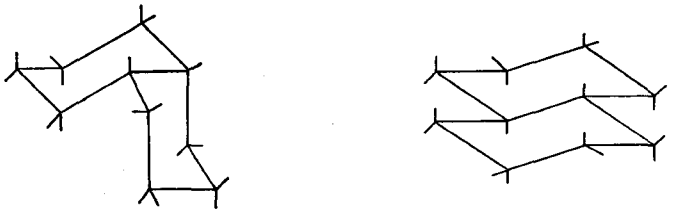
XI XII XIII *cis*- XIV *trans*-

Fig. 7 shows the original diagrammatical method of representing *cis*-decalin by the fusion of two boat forms of *cyclo*hexane, and *trans*-decalin by the fusion of two chair forms; these are the forms suggested by Mohr.

cis-decalin *trans*-decalin

FIG. 4.7.

The configurations of the decalins, however, are now known to be more complicated than this, the complication arising from the fact that a number of strainless modifications are possible, which differ in the type of " locking ", *i.e.*, whether axial or equatorial bonds are used to fuse the rings. According to Hassel *et al.* (1946), *cis*- and *trans*-decalins are as shown in Fig. 8; the



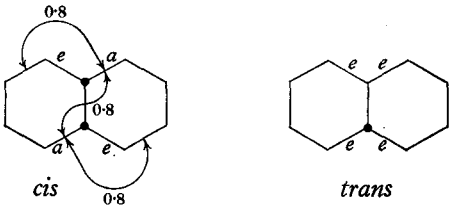
cis-decalin *trans*-decalin

FIG. 4.8.

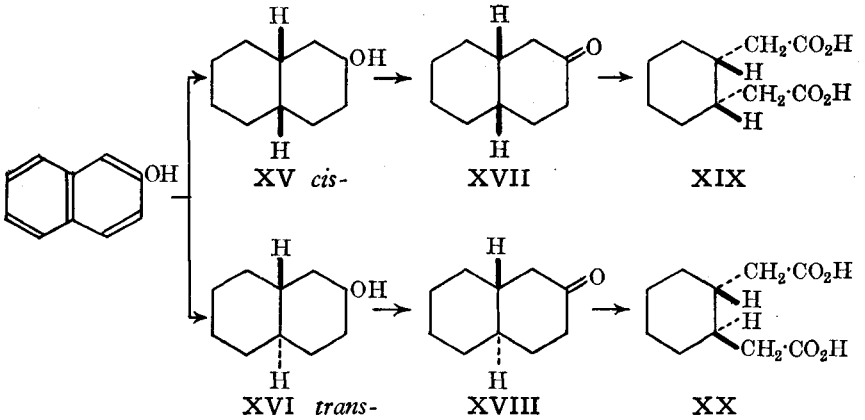
cis-form is produced by joining one axial and one equatorial bond of each ring, whereas the *trans*-form is produced by joining the two rings by equatorial bonds only; in both cases the *cyclo*hexane rings are all chair forms (see also below).

Johnson (1953) has calculated the difference in energy content between these two forms in the following simple manner. The *trans*-form is arbitrarily assigned a value of zero energy, and when this form is compared with the *cis*, it will be found that the latter has three extra skew interactions involving the two axial bonds (this is shown in the following diagram; the *cis*-form has 3 staggered and 15 skew arrangements, and the *trans*-form 6 staggered and 12 skew). Since each of these skew interactions is associated with an energy increase of 0·8 kg.cal., the total energy difference between the *cis*- and *trans*-forms is $3 \times 0{\cdot}8 = 2{\cdot}4$ kg.cal. This value agrees well with that of Rossini *et al.* (1960) from measurements of heat of combustion.

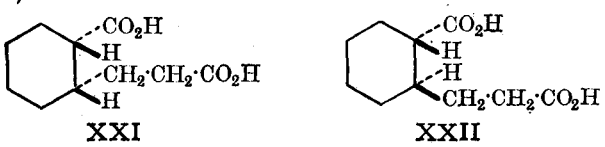
It might be noted, in passing, that if these two decalins are regarded as 1 : 2-disubstituted *cyclo*hexanes, then the *trans*-form (*e* : *e*) would be expected to be more stable than the *cis*- (*e* : *a*).



We shall now deal with the determination of configuration in the decalin series. The configurations may be ascertained by using the Auwers–Skita rule (see §5. (x)*b*). Hückel (1923, 1925), however, isolated two forms of 2-decalol and determined their configurations by the following chemical methods. 2-Naphthol, on hydrogenation in the presence of nickel as catalyst, gave two 2-decalols, XV and XVI, each of which, on oxidation with chromic acid, gave a decal-2-one (XVII and XVIII). These two decalones each gave, on oxidation with permanganate, a *cyclo*hexane-1 : 2-diacetic acid. These diacetic acids were geometrical isomers; one was resolvable and therefore must be the *trans*-isomer, XX; and the other, which was not resolvable, must therefore be the *cis*-isomer, XIX (this is the *meso*-form). Thus the configurations of the two decalols and the two decalones are established:

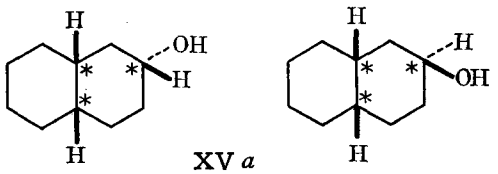


In addition to the two *cyclo*hexane-1 : 2-diacetic acids (which are formed by scission of the 2 : 3-bond of the decalone), two other geometrical isomers were also obtained, *viz.* *cis*- and *trans-cyclo*hexane-1-carboxyl-2-propionic acids, XXI and XXII (these are formed by scission of the 1 : 2-bond of the decalone).

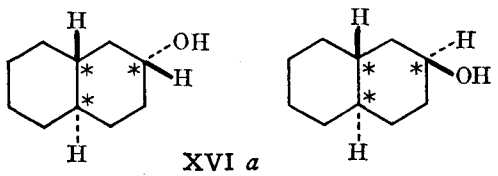


The conversion of 2-naphthol into two decalols does not prove that the two decalols are the *cis*- and *trans*-isomers described above. It is possible that both compounds could have been the *cis*- and *trans*-forms of a *given* decalol; since the carbon atom of the CHOH group in the 2-decalol is asym-

metric, it can exist in *two* configurations, *i.e.*, each decalol, XV and XVI, can exist in two forms; XV*a* and XVI*a*. Had the two decalols been the



XV *a*



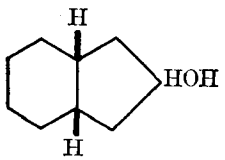
XVI *a*

two forms of either XV or XVI, then on their oxidation, only *one* decalone would have been produced. Since, however, *two* decalones were obtained, the two decalols must be of the types XV and XVI—one of each, or even a mixture of the pairs; further proof of the existence of the types XV and XVI lies in the fact that the two decalones gave geometrical isomers of *cyclo*hexane-1 : 2-diacetic acid.

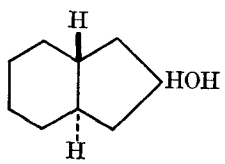
Consideration of formulæ XV*a* and XVI*a* shows the presence of three asymmetric carbon atoms in each of the four possible forms, and since all four possess no elements of symmetry, four pairs of enantiomorphs should be possible theoretically. Actually all eight forms have been isolated, but their configurations have not yet been established with certainty.

There are only *two* geometrical isomers possible for the decalins, and their configurations have been established by the reduction of the two decalones, XVII and XVIII, by means of the Wolff–Kishner method (Eisenlohr *et al.*, 1924; see also Vol. I); each decalone gives the corresponding decalin. It is interesting to note in this connection that Willstätter *et al.* (1924) found that hydrogenation of naphthalene in the presence of platinum black as catalyst gives mainly *cis*-decalin, whereas in the presence of nickel as catalyst the main product is *trans*-decalin. The configurations of the decalins have also been determined by means of their NMR spectra (see also end of this section).

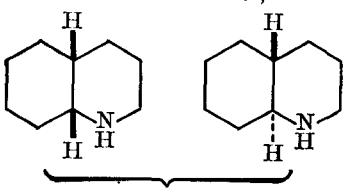
Various other fused ring systems have also been shown to exhibit the



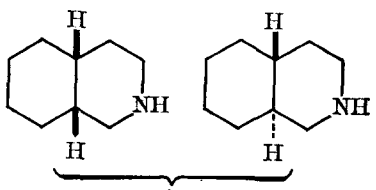
cis-hydrindanol. Two forms; both *meso*-



trans-hydrindanol. Resolvable



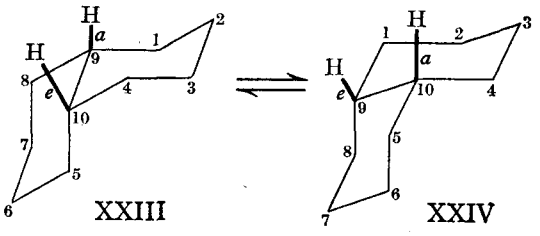
Decahydroquinolines



Decahydro*iso*quinolines

same type of geometrical isomerism as the decalins, *e.g.*, the hydrindanols exist in *cis*- and *trans*-forms (Hückel *et al.*, 1926), and also the decahydroquinolines and decahydro*iso*quinolines (Helfer *et al.*, 1923, 1926).

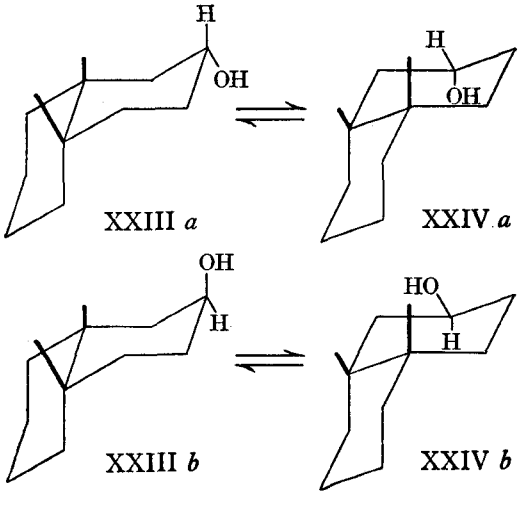
It has already been pointed out that in monosubstituted *cyclo*hexanes, the preferred conformation is the one with the substituent equatorial, but owing to the low energy barrier between this and the axial form, the two are readily interconvertible. In the case of the monosubstituted decalins, the problem is more complicated. In *cis*-decalin, since ring fusion involves equatorial and axial bonds, the molecule is flexible and can interchange with the other *cis*-form, *i.e.*, there are two *cis*-forms possible (XXIII and XXIV), and these are identical and in equilibrium (*cf. cyclo*hexane). This has been shown to be so by Hassel (1950); thus:



As pointed out above, Musher *et al.* (1958) distinguished between *cis*- and *trans*-decalin by means of their NMR spectra. The former gives a sharp band whereas the latter gives a broad spectrum. These differences are due to the former molecule undergoing relatively rapid interconversion between the two conformations, whilst the latter molecule has a more rigid structure and hence the axial and equatorial hydrogen atoms are distinguishable (and so give a broad spectrum).

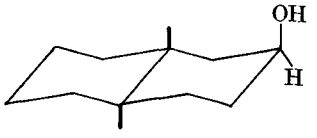
Now let us consider *cis*-2-decalol. Here there are four possible conformations which, in pairs, are in equilibrium. Two arise from XXIII (XXIII*a* and XXIII*b*), and two from XXIV (XXIV*a* and XXIV*b*).

In XXIII*a* and XXIV*b* the hydroxyl group is equatorial, and so these two conformations contain about the same energy. In XXIV*a* and XXIII*b* the hydroxyl group is axial, and on the basis that an equatorial conformation is more stable than an axial, then XXIII*a* and XXIV*b* will contribute

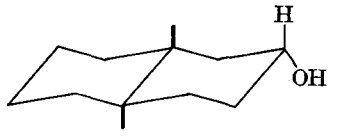


more to the actual state of the molecule than will XXIV*a* and XXIII*b*, *i.e.*, the hydroxyl group in *cis*-2-decalol should possess more equatorial character than axial. It is also interesting to note that the two axial forms do not contain the same energy. In XXIII*b* the *a*-hydroxyl group is involved in the normal 1 : 3-hydrogen interactions (at 4 and 9), but in XXIV*a* the interaction is the normal 1 : 3- with the hydrogen at 4 and the larger 1 : 3-interaction with the CH_2 group at 8. Thus XXIV*a* should be less stable than XXIII*b*.

In *trans*-decalin there is only one stable conformation, since the ring fusions use equatorial bonds. If the molecular conformation were "inverted", the two ring fusions would now have to be axial, and this type of fusion is impossible (the axial bonds on adjacent carbon atoms are pointing in *opposite* directions). Thus, in *trans*-2-decalol, there are only two conformations possible, XXV and XXVI. Furthermore, the latter, with



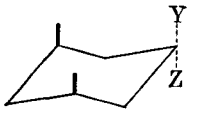
XXV



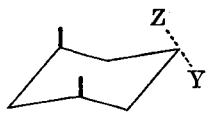
XXVI

the equatorial-hydroxyl conformation, would be expected to be more stable than the former (with the axial hydroxyl).

§12. Effect of conformation on the course and rate of reactions. Since the environments of axial and equatorial groups are different, it may be expected that the reactivity of a given group will depend on whether it is axial or equatorial. Now S_N2 reactions always occur with inversion (§4. III). Hence if the geometry of the molecule is such as to hinder the approach of the attacking group (Z) along the bonding line remote from the group to be expelled (Y), then the S_N2 reaction will be slowed down. Examination of formulæ I and II shows that the transition state for an S_N2 reaction is more readily formed when Y is axial (I) than when it is equatorial (II). In I, the approach of Z is unhindered and the expulsion



I



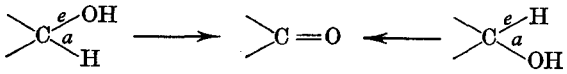
II

of Y assisted by the normal 1 : 3-interactions. In II, the approach of Z is hindered by the rest of the ring. Thus S_N2 reactions take place more readily with an axial substituent than with an equatorial.

The study of S_N1 reactions in *cyclo*hexane derivatives is made difficult because of the ease with which elimination reactions usually occur at the same time. It can be expected, however, that an S_N1 reaction will be sterically accelerated for an axial substituent, since the formation of a carbonium ion will relieve the steric strain due to 1 : 3-interactions. On the other hand, since these 1 : 3-interactions are absent for an equatorial substituent, no steric acceleration will operate in this conformation.

A particularly important substituent group in cyclic compounds is hydroxyl, and two very important reactions in which this group is involved are esterification and hydrolysis (of the ester). Owing to the hindered character of an axial group due to 1 : 3-interactions, esterification and hydrolysis will occur more readily with the equatorial conformation. In

the same way, esterification and hydrolysis of esters in which a carboxyl group is the substituent will also occur more readily when this group is equatorial. On the other hand, the relative rates of oxidation of secondary *a*- and *e*-alcohols to ketones by chromic acid (or hypobromous acid) is the reverse of the relative rates of hydrolysis of their carboxylic esters, *i.e.*, an *a*-hydroxyl is more readily oxidised than an *e*-. The reason for this is that the rate-determining step in this oxidation is a direct attack on the hydrogen atom of the C—H bond. If the hydroxyl is axial, the hydrogen is equatorial, and *vice versa*; thus:

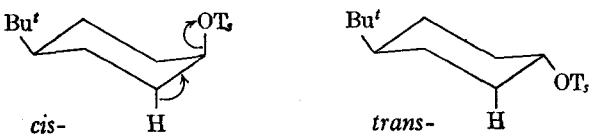


Elimination reactions are also of great importance in cyclic compounds. As we have seen (§5b), in ionic E2 reactions the four centres involved lie in a plane. In *cyclo*hexane systems this geometrical requirement is only found in *trans*-1 : 2-diaxial compounds, and these compounds thus undergo ready elimination reactions. In rigid systems, *e.g.*, the *trans*-decalin type, elimination in *trans*-1 : 2-diequatorial compounds is slower than in the corresponding diaxial compounds. *cis*-1 : 2-Compounds (in which one substituent must be axial and the other equatorial) undergo elimination reactions slowly.

The steric course of E1 reactions is more difficult to study than that of E2 reactions because of the two-stage mechanism. This makes it difficult to ascertain the geometry of the intermediates involved. The formation of the carbonium ion will be sterically accelerated if the ionising group is axial and, if a second group is eliminated to form a double bond, this second stage will also be sterically accelerated if the second group is axial. Barton *et al.* (1951) have pointed out various examples in which E1 reactions are favoured by the diaxial conformation.

The arguments used above are satisfactory so long as we know whether the group under discussion is axial or equatorial. Since, however, the two chair forms are readily interconvertible and in equilibrium, to study these predictions experimentally it is necessary to deal with " rigid " conformations. The *t*-butyl group, because of its large size, is far more stable in the *e*- than in the *a*-position (the energy difference between the two forms is about 5·6 kg.cal./mole; Winstein *et al.*, 1955). Thus almost only the *e*-form is present and consequently this position is " locked ". Therefore 4-substituents must be axial when *cis* to the *t*-butyl group and equatorial when *trans* to this group (§11). Working with different substituents in the 4-position with respect to the *t*-butyl group, various workers have confirmed the above predictions experimentally, *e.g.*, it has been shown that *cis*-4-*t*-butyl*cyclo*hexanol forms esters more slowly than the *trans*-isomer, and similarly *cis*-4-*t*-butyl*cyclo*hexane-1-carboxylic acid is more slowly esterified and the ester more slowly hydrolysed than the *trans*-isomer.

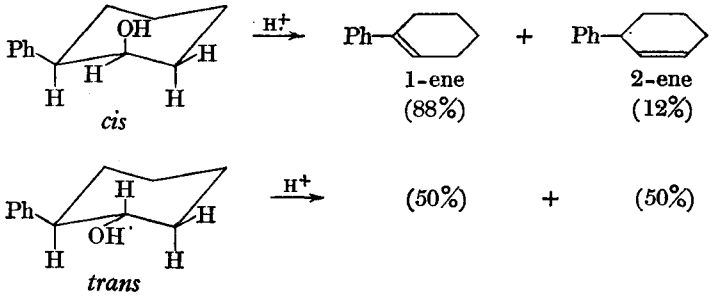
Another interesting example is the case of 4-*t*-butyl*cyclo*hexyl tosylate (Eliel *et al.*, 1956). Two forms are possible, *cis* and *trans*, but because of the large bulk of the *t*-butyl group, this group is always equatorial. Under



the same conditions (sodium ethoxide in ethanol at 70°), the *cis*-form readily undergoes bimolecular elimination (E2), but the *trans*- does not. The latter, however, does undergo unimolecular (E1) elimination.

Some examples of neighbouring group participation in *cyclo*hexane systems have been described in Ch. III (§§6b, 6c, 6d). These examples clearly show the effect of conformation on rates of reaction when anchimeric assistance is possible.

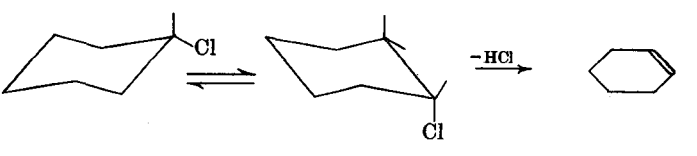
Not only does conformation control the rate of reactions, but it also may affect the course of a reaction. An example of the latter effect is the elimination reaction undergone by 2-phenyl*cyclo*hexanol in the presence of phosphoric acid to form phenyl*cyclo*hexene. Price *et al.* (1940) have shown that both the *cis* and *trans* alcohols are dehydrated, the former more readily than the latter. The product was shown to be a mixture of phenyl*cyclo*hex-1- and 2-ene, the former predominating when the *cis*-alcohol was used, and both olefins being present in about equal amounts when the *trans*-alcohol was used. The reaction has been shown to proceed by the E1 mechanism, but the reason for the different proportions of olefins is uncertain.



Another example of the effect of conformation on the course of a reaction in *cyclo*hexane systems is the action of nitrous acid on amines. Mills (1953) has proposed the following generalisation: When the amino-group is equatorial, the product is an alcohol with an equatorial conformation; but when the amino-group is axial, the main product is an olefin together with some equatorial alcohol.

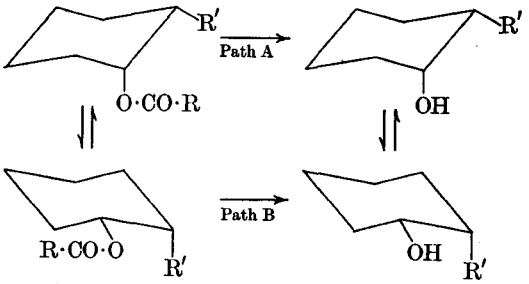
Just as *trans* elimination is favoured with the two groups axial and *trans*, so it has been found that addition of electrophilic reagents to a double bond in *cyclo*hexenes is predominantly diaxial.

As we have seen, although there is a preferred form in *cyclo*hexane derivatives, the energy of interconversion between the preferred and less stable form is too low to permit their being distinguished by the classical methods of stereochemistry. This predominance of the preferred form holds good at room temperature (or below). At higher temperatures, or during the course of a chemical reaction, the preponderance of the preferred form may be reduced. In chemical reactions, it may be possible for the reaction to proceed more readily through the less stable conformation because it is this one which more closely approaches the geometry of the transition state. An example of this type if chloro*cyclo*hexane. As we have seen, the preferred form is the equatorial conformation. This compound, on treatment with ethanolic potassium hydroxide, undergoes dehydrohalogenation to form *cyclo*hexene. Since *trans* elimination is preferred, the reaction probably proceeds *via* the axial form.



Allinger *et al.* (1961) have examined the conformations of the 2-halo*cyclo*hexanones by polarographic methods. It was suggested that since these compounds are polarographically reduced (Elving *et al.*, 1956), it seems likely that the reduction potential of such a system will depend on the conformation of the halogen atom. This prediction was shown to be the case in practice. The authors showed that for systems with relatively fixed conformation, such as the 2-halo-4-*t*-butyl*cyclo*hexanones, the epimer with the axial halogen is reduced more easily. Furthermore, it was found that a flexible molecule such as 2-chloro*cyclo*hexanone, which contains *comparable* amounts of the two conformations, showed the potential characteristic of the more easily reduced (axial) form. This is understandable on the basis that the *e*-form is very readily converted into the *a*-form, the rate of the conversion being rapid compared with the rate of the reduction.

Now let us consider reactions involving the hydroxyl group. It has already been pointed out that equatorial hydroxyl groups are more readily esterified, and equatorial esters more readily hydrolysed, than when these groups are axial. If an axial ester group has to stay in this position during hydrolysis, then because of the steric hindrance (1 : 3-interactions), the rate will be relatively slow (reaction path A). It is possible, however, that prior to reaction, the molecule is forced into the equatorial conformation (*cf.* chloro*cyclo*hexane above). If this were to happen, then the slower rate of hydrolysis would be due to the additional energy required to bring about the change in conformation (reaction path B).



Experimental data has enabled one path to be distinguished from the other (see also §16. VIII).

In *fused systems*, owing to the rigidity of the structure, such interconversions (as described above) are far less likely to occur.

In this chapter, the discussion of conformational analysis has been applied to *cyclo*hexane and its derivatives, and this has been done in order to introduce some of the ideas connected with this problem. The generalisations applicable to *cyclo*hexane compounds, however, are also applicable to heterocyclic compounds containing nitrogen, oxygen or sulphur (see, *e.g.*, tropines, §22. XIV; carbohydrates, §7h. VII). They are also applicable to the polynuclear compounds, *e.g.*, the Steroids; in fact, much of the work leading to these generalisations has been carried out on these compounds (see §4c. XI).

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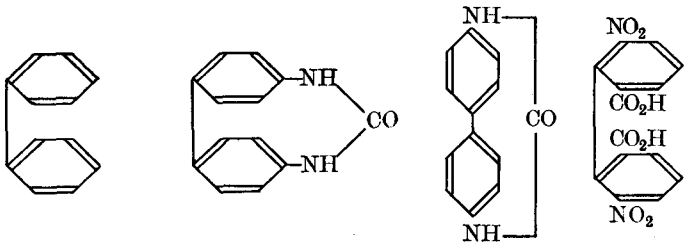
CHAPTER V

STEREOCHEMISTRY OF DIPHENYL COMPOUNDS

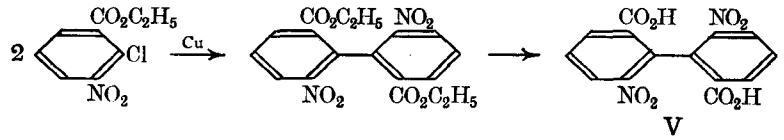
§1. Configuration of the diphenyl molecule. If we assume that the benzene ring is planar, then the diphenyl molecule will consist of two planar rings; but without any further information we cannot say how these two rings are arranged spatially. Kaufler (1907) proposed the "butterfly" formula, I, in order to account for the chemical behaviour of various diphenyl derivatives, *e.g.*, Michler and Zimmermann (1881) had condensed



I II III IV

benzidine with carbonyl chloride and obtained a product to which Kaufler assigned structure II. According to Kaufler, the co-axial structure III was impossible, since the two amino-groups are too far apart to react simultaneously with carbonyl chloride; it should be noted that this *simultaneous* reaction at both ends was assumed by Kaufler. Simultaneous reaction, however, is reasonable (according to Kaufler) on the folded structure, II.

Now Schultz (1880) had prepared a dinitrodiphenic acid by the nitration of diphenic acid, and Schmidt *et al.* (1903), from their work on this acid, believed it to be 6 : 6′-dinitrodiphenic acid, IV; these workers, it should be noted, did not synthesise the acid. In 1921, however, Kenner *et al.* synthesised 6 : 6′-dinitrodiphenic acid by means of the Ullmann reaction (see Vol. I) on the ethyl ester of 2-chloro-3-nitrobenzoic acid, and hydrolysing the product. This acid, V (written with the two benzene rings co-axial), did not have the same melting point as Schultz's acid, and so Kenner, believing that his and Schultz's acid were both 6 : 6′-dinitrodiphenic acid, suggested that the two were stereoisomers. Then Christie and Kenner



V

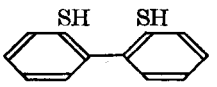
(1922) showed that Kenner's acid was resolvable, and pointed out that this could be explained on the Kaufler formula, IV, since this structure has no elements of symmetry. These authors, however, also pointed out that the optical activity could also be accounted for by the co-axial structure, V, provided that the two benzene rings do not lie on one plane (see also §2).

Kaufler's formula, as we have seen, was based on the assumption that the two amino-groups in benzidine react *simultaneously* with various reagents. Re-investigation of these reactions showed that this was not the case, *e.g.*, Turner and Le Fèvre (1926) found that the compound produced from

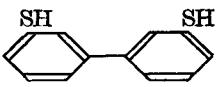
benzidine and carbonyl chloride was not as originally formulated (see II or III), but had a free amino-group, *i.e.*, the compound was

$$[NH_2 \cdot C_6H_4 \cdot C_6H_4 \cdot NH]_2CO.$$

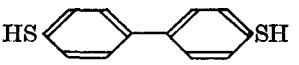
Hence Kaufler's *reason* for his butterfly formula is incorrect, and although it does not necessarily follow that the *formula* is incorrect, nevertheless Turner's work weakened Kaufler's claim. One of the strongest bits of chemical evidence for rejecting Kaufler's formula is that of Barber and Smiles (1928). These workers prepared the three dimercaptodiphenyls, VI, VII and VIII, and oxidised each one. Only one of them, the 2 : 2'-



VI



VII



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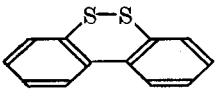


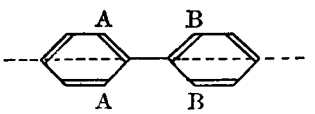
IX

derivative, VI, gave the intramolecular disulphide (diphenylene disulphide, IX). On the Kaufler formula, all three dithiols would be expected to give the intramolecular disulphides, since the two thiol groups are equally distant in all three compounds.

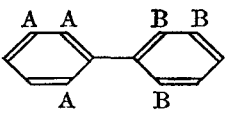
Physico-chemical methods have also been used to determine the configuration of the diphenyl molecule, *e.g.*, the crystal structure of **4 : 4'**-diphenyl derivatives shows a centre of symmetry; this is only possible for the co-axial formula. Dipole moment measurements also confirm this configuration, *e.g.*, the dipole moment of **4 : 4'**-dichlorodiphenyl is zero; this again is only possible if the two benzene rings are co-axial.

§2. Optical activity of diphenyl compounds. Christie and Kenner's work (see above) has been extended by other workers, who showed that compounds in which at least *three* of the four *ortho*-positions in diphenyl are occupied by certain groups could be resolved. It was then soon found that two conditions were necessary for diphenyl compounds to exhibit optical activity:

(i) Neither ring must have a vertical plane of symmetry. Thus I is not resolvable, but II is.



I

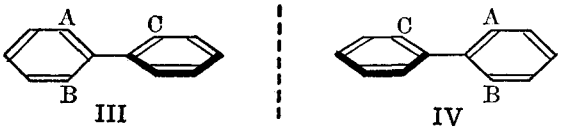


II

(ii) The substituents in the *ortho*-positions must have a large size, *e.g.*, the following compounds were resolved: 6-nitrodiphenic acid, **6 : 6'**-dinitrodiphenic acid, **6 : 6'**-dichlorodiphenic acid, **2 : 2'**-diamino-**6 : 6'**-dimethyldiphenyl (see also §4).

The earlier work showed that three groups had to be present in the *ortho*-positions. This gave rise to the theory that the groups in these positions impinged on one another when free rotation was attempted, *i.e.*, the steric effect prevented free rotation. This theory of restricted rotation about the single bond joining the two benzene rings (in the co-axial formula) was suggested simultaneously in 1926 by Turner and Le Fèvre, Bell and Kenyon,

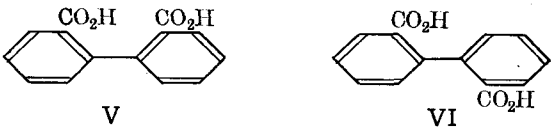
and Mills. Consider molecule III and its mirror image IV. Provided that the groups A, B and C are large enough to "interfere mechanically", *i.e.*, to behave as "obstacles", then free rotation about the single bond is



III IV

restricted. Thus the two benzene rings cannot be coplanar and consequently IV is not superimposable on III, *i.e.*, III and IV are enantiomorphs. In molecule III there is no asymmetric carbon atom; it is the molecule *as a whole* which is asymmetric, due to the restricted rotation.

In diphenyl the two benzene rings are co-axial, and in optically active diphenyl derivatives the rings are inclined to each other due to the steric and repulsive effects of the groups in the *ortho*-positions. The actual angle of inclination of the two rings depends on the nature of the substituent groups, but it appears to be usually in the vicinity of 90°, *i.e.*, the rings tend to be approximately perpendicular to each other. Thus, in order to exhibit optical activity, the substituent groups in the *ortho*-positions must

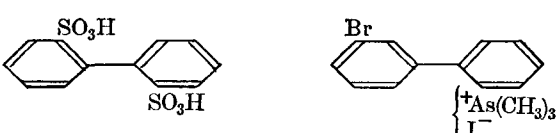


V VI

be large enough to prevent the two rings from becoming coplanar, in which case the molecule would possess a plane or a centre of symmetry, *e.g.*, diphenic acid is not optically active. In configuration V the molecule has a plane of symmetry, and in configuration VI a centre of symmetry; of these two, VI is the more likely because of the repulsion between the two carboxyl groups (*cf.* §4. II).

If restricted rotation in diphenyl compounds is due entirely to the spatial effect, then theoretically we have only to calculate the size of the group in order to ascertain whether the groups will impinge and thereby give rise to optical activity. In practice, however, it is found that groups (and atoms) behave as if they were larger than the volumes obtained from group (and atomic) radii (*cf.* §15b. I). This behaviour is largely due to the fact that groups also repel (or attract) one another because of the electric charges that are usually present on these groups. Thus the actual distance that the atoms or groups (in the *ortho*-positions) can approach one another is *greater* than that obtained from the atomic and group radii. Better agreement with experiment is obtained when the van der Waals radii (§2. I) are used for calculating the "size" of a group.

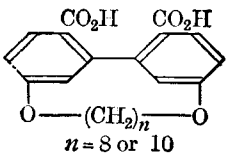
Later work has shown that if the substituent groups are large enough, then only *two* in the *o*- and *o'*-positions will produce restricted rotation, *e.g.*, Lesslie and Turner (1932) resolved diphenyl-2 : 2'-disulphonic acid, VII. In this molecule the sulphonic acid group is large enough to be impeded by the *ortho*-hydrogen atoms. Lesslie and Turner (1933) have also resolved



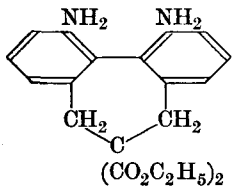
VII VIII

the arsonium compound VIII; here also the trimethylarsonium group is large enough to be impeded by the *ortho*-hydrogen atoms (the bromine atom in the *meta*-position gives asymmetry to this ring). This example is unique up to the present in that only *one* substituent in the *ortho*-position produces optical activity in diphenyl compounds.

It has already been pointed out that diphenic acid is not optically active, and that its configuration is most probably VI. Now calculation shows that the effective diameter of the carboxyl group is large enough to prevent configuration V from being planar, and consequently, if the two rings could be held more or less in this configuration, the molecule would not be coplanar and hence would be resolvable. Such a compound, IX, was prepared and resolved by Adams and Kornblum (1941). The two benzene



IX



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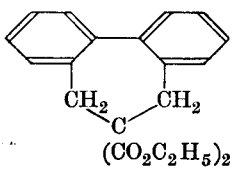
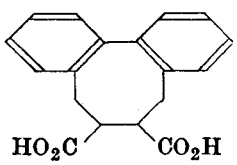
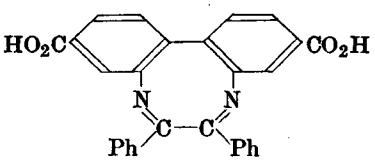


XI

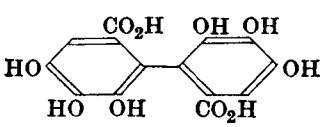
rings are not coplanar and are held fairly rigid by the large methylene ring. Iffland *et al.* (1956) have also prepared the optically active diphenyl X which has a 2 : 2′-bridge and two amino-groups in the 6 : 6′-positions. On the other hand, these authors have also prepared XI in optically active forms; this compound has the 2 : 2′-bridge but no substituents in the 6 : 6′-positions. Mislow (1957) has also obtained the dibenzo*cyclo*-octadiene acids, XII, in optically active forms; both forms were highly optically labile. Similar to



XII

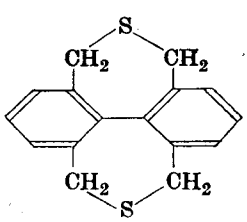


XIII



XV

XII is XIII which has been resolved by Bell (1952). Mislow *et al.* (1961) have also resolved the diphenyl derivative XIV.



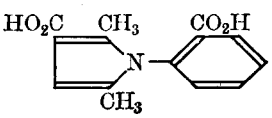
XIV

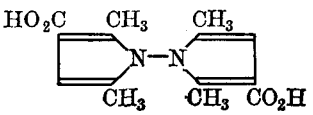
A point of interest in connection with optically active diphenyls is that Schmidt *et al.* (1957) have shown that XV occurs naturally in an optically active form.

§2a. Absolute configurations of diphenyls. Mislow *et al.* (1958) have determined the absolute configuration of 6 : 6′-dinitro-2 : 2′-diphenic acid. Their method was chemical; assignment of absolute configuration has been obtained from a consideration of the transition states in the Meerwein–Ponndorf–Verley reduction of a dissymmetric diphenylic ketone by asymmetric alcohols of known absolute configuration (*cf.* §7. III). Using this diphenyl as absolute standard, Mislow *et al.* (1958) then correlated configurations in the diphenyl series by the quasi-racemate method (§9a. II). In this way these authors determined the configurations of 6 : 6′-dichloro- and 6 : 6′-dimethyl-2 : 2′-diphenic acid. Mislow *et al.* (1960) have also confirmed absolute configurations in the diphenyl series by the rotatory dispersion method (§12a. I).

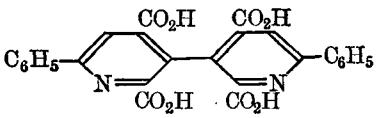
§3. Other examples of restricted rotation. In addition to the diphenyl compounds, there are many other examples where optical activity in the molecule is produced by restricted rotation about a single bond which may or may not be one that joins two rings. The following examples are only a few out of a very large number of compounds that have been resolved.

(i) Adams *et al.* (1931) have resolved the following *N*-phenylpyrrole and *N* : *N*′-dipyrryl.

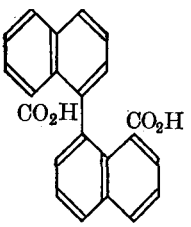




Adams *et al.* (1932) have also resolved the 3 : 3′-dipyridyl



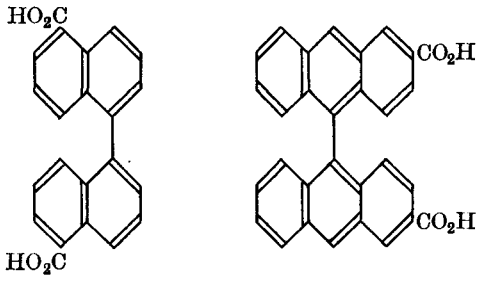
(ii) 1 : 1′-Dinaphthyl-8 : 8′-dicarboxylic acid has been obtained in optically active forms by Stanley (1931).



This compound gives rise to asymmetric transformation (§10 iv. II); resolution with brucine gave 100 per cent. of either the (+)- or (−)-compound.

Other compounds similar to the dinaphthyl which have been obtained in optically active forms are 1 : 1′-dinaphthyl-5 : 5′-dicarboxylic acid, I (Bell *et al.*, 1951), the dianthryl derivatives, II and III (Bell *et al.*, 1949), and the 4 : 4′- and 5 : 5′-diquinolyls, IV and V (Crawford *et al.*, 1952).

(iii) Mills and Elliott (1928) obtained *N*-benzenesulphonyl-8-nitro-1-naphthylglycine, VI, in optically active forms; these were optically unstable,



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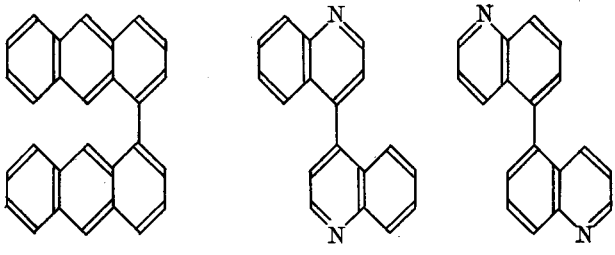
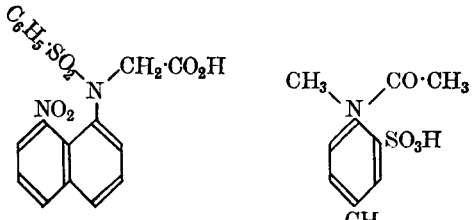


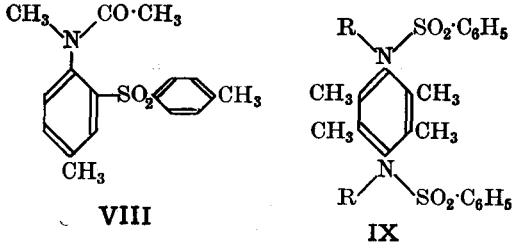
III IV V

undergoing asymmetric transformation with brucine. Mills and Kelham (1937) also resolved *N*-acetyl-*N*-methyl-*p*-toluidine-3-sulphonic acid, VII, with brucine, and found that it racemised slowly on standing. In both

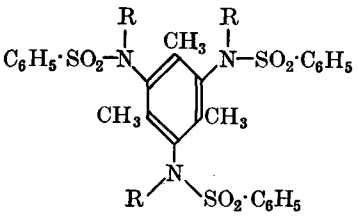


VI VII

VI and VII the optical activity arises from the restricted rotation about the C—N bond (the C being the ring carbon to which the N is attached). Asymmetry arising from the same cause is also shown by 2-acetomethylamido-4′ : 5-dimethyldiphenylsulphone, VIII; this was partially resolved by Buchanan *et al.* (1950; see also §10 iv. II). It is also interesting to note in this connection that Adams *et al.* (1950) have isolated pairs of *geometrical* isomers of compounds of the types IX and X; here geometrical isomerism is possible because of the restricted rotation about the C—N bonds.

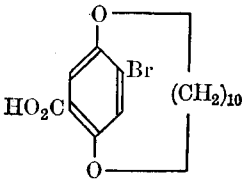


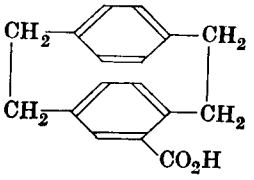
VIII IX



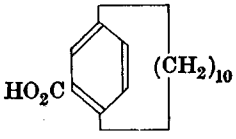
X

(iv) Lüttringhaus *et al.* (1940, 1947) isolated two optically active forms of 4-bromogentisic acid decamethylene ether. In this compound the methylene ring is perpendicular to the plane of the benzene ring; the two substituents, Br and CO_2H, prevent the rotation of the benzene nucleus inside



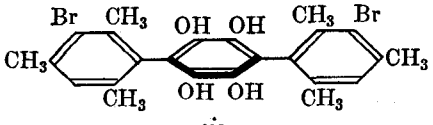


the large ring. Cram *et al.* (1955) have obtained a paracyclophane in optically active forms; there is insufficient space to allow the benzene ring carrying the carboxyl group to rotate to give the enantiomorph. In this compound the two benzene rings are parallel and perpendicular to the plane

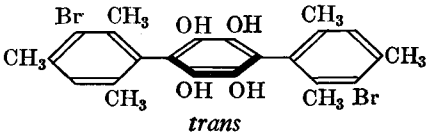


of the ring. On the other hand, Blomquist *et al.* (1961) have resolved the simple paracyclophane shown.

(v) Terphenyl compounds can exhibit both geometrical and optical isomerism when suitable substituents are present to prevent free rotation about single bonds, *e.g.*, Shildneck and Adams (1931) obtained the following compound in both the *cis*- and *trans*-forms.

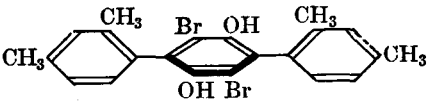


cis

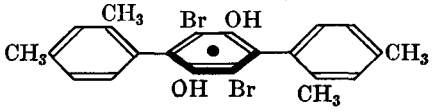


trans

Interference of the methyl and hydroxyl groups in the *ortho*-positions prevents free rotation and tends to hold the two outside rings perpendicular to the centre ring. Inspection of these formulæ shows that if the centre ring does not possess a vertical plane of symmetry, then optical activity is



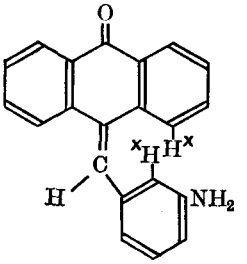
cis



trans

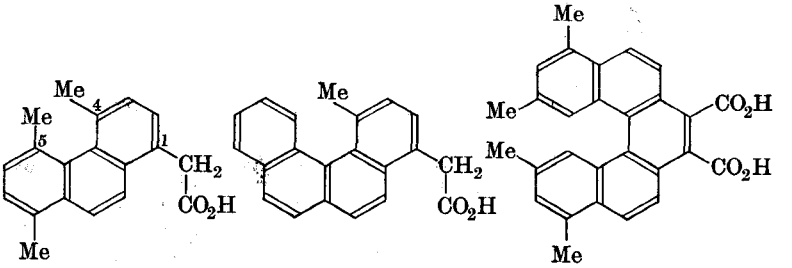
possible. Thus Browning and Adams (1930) prepared the dibromo *cis*- and *trans*-forms, and resolved the *cis*-isomer; the *trans*-isomer is not resolvable since it has a centre of symmetry.

(vi) A very interesting case of restricted rotation about a single bond is afforded by the compound 10-*m*-aminobenzylideneanthrone. This was prepared by Ingram (1950), but he failed to resolve it. He did show, however,



that it was optically active by the mutarotation of its camphorsulphonate salt, and by the preparation of an active hydriodide. Thus the molecule is asymmetric, and this asymmetry can only be due to the restricted rotation of the phenyl group about the C—phenyl bond, the restriction being brought about by *hydrogen* atoms in the *ortho*-positions. The two hydrogen atoms labelled $H^{\times}$ overlap in space, and consequently the benzene ring cannot lie in the same plane as the 10-methyleneanthrone skeleton.

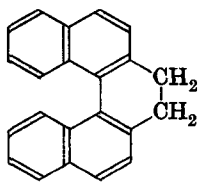
§3a. Molecular overcrowding. All the cases discussed so far owe their asymmetry to restricted rotation about a single bond. There is, however, another way in which steric factors may produce molecular asymmetry. It has been found that, in general, non-bonded carbon atoms cannot approach



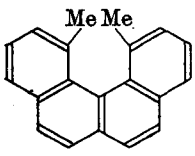
I II III

closer to each other than about 3·0 A. Thus, if the geometry of the molecule is such as to produce "intramolecular overcrowding", the molecule becomes distorted. An example of this type is 4 : 5 : 8-trimethyl-1-phenanthrylacetic acid, I. The phenanthrene nucleus is planar and substituents

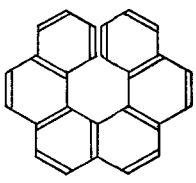
lie in this plane. If, however, there are fairly large groups in positions 4 and 5, then there will not be enough room to accommodate both groups in the plane of the nucleus. This leads to strain being produced by intramolecular overcrowding, and the strain may be relieved by the bending of the substituents out of the plane of the nucleus, or by the bending (buckling) of the aromatic rings, or by both. Thus the molecule will not be planar and consequently will be asymmetric and therefore (theoretically) resolvable. Newman *et al.* (1940, 1947) have actually partially resolved it, and have also partially resolved II and III (both of which also exhibit out-of-plane distortions). All of these compounds were found to have low optical stability, but Turner *et al.* (1955) have prepared the optically active forms of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene (IV), which is more



IV



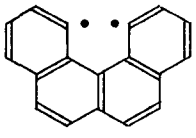
V



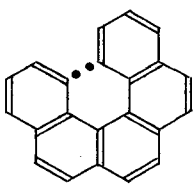
VI

optically stable than I, II and III. Newman *et al.* (1955, 1956) have prepared V and VI which, so far, are the most optically stable compounds of the intramolecular overcrowding type.

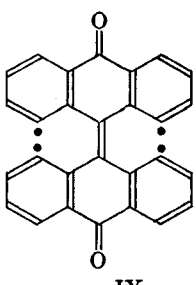
It will be noticed that in IV and VI the only way in which out-of-plane distortion can occur is through buckling of the molecule. The simplest



VII



VIII



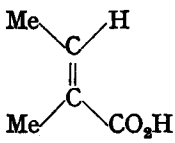
IX

molecule exhibiting overcrowding and consequent *out-of-plane buckling* of the molecule is 3 : 4-benzophenanthrene (VII); this has been shown to be non-planar by X-ray analysis (Schmidt *et al.*, 1954). Similarly, Robertson *et al.* (1954) have shown that VIII exhibits out-of-plane buckling.

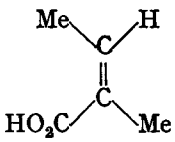
Another point to note in connection with out-of-plane buckling is that the buckling is distributed over all the rings in such a manner as to cause the minimum distortion in any one ring. This distortion, which enables non-bonded carbon atoms to avoid being closer together than 3·0 A (marked with dots in VII and VIII), forces some of the other carbon atoms to adopt an almost tetrahedral valency arrangement (the original hybridisation is trigonal), and this affects the physical and chemical properties of the molecule, *e.g.*, Coulson *et al.* (1955) have calculated that the deformation in VIII produces a loss of resonance energy of about 18 kg.cal./mole.

Just as benzene rings may suffer distortion, so can a molecule which owes its planarity to the presence of a double bond. Such an example is dianthronylidene (IX). The carbon atoms marked with dots are overcrowded (the distance between each pair is 2·9 A), and the strain is relieved by a

rotation of about 40° around the olefinic double bond (Schmidt *et al.*, 1954). Even in such simple molecules as tiglic acid (X) the two methyl groups give rise to molecular overcrowding with the result that the β-methyl group



X



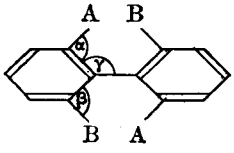
XI

appears to be displaced from the molecular plane, thereby relieving overcrowding which is also partly relieved by small distortions in bond angles. These results were obtained by Robertson *et al.* (1959) from X-ray studies, and these authors also showed similar distortions in angelic acid (XI).

In polynuclear aromatic hydrocarbons in which the strain tends to be overcome by out-of-plane displacements of substituents and out-of-plane ring buckling, these effects cause changes in the ultraviolet spectra, but it is not yet possible to formulate any correlating rules. NMR studies by Ried (1957) have shown a shift for the hydrogen atoms in positions 4 and 5 in phenanthrene itself. A similar phenomenon has been detected by Brownstein (1958) in 2-halogenodiphenyls, and the explanation offered is that the shift is due to the steric effect between the 2-halogen and the 2′-hydrogen atom.

Although molecular overcrowding is normally confined in the polynuclear type to systems containing three or more rings, nevertheless various substituted benzenes may also exhibit out-of-plane displacements of the substituents. Electron-diffraction studies of polyhalogenobenzenes suggest that such molecules are non-planar (Hassel *et al.*, 1947), whereas X-ray studies indicate that in the solid state such molecules are very closely or even exactly planar (Tulinsky *et al.*, 1958; Gafner *et al.*, 1960). Ferguson *et al.* (1959, 1961) have examined, by X-ray analysis, polysubstituted benzenes containing not more than one halogen atom, *e.g.*, *o*-chloro- and bromobenzoic acid, and 2-chloro-5-nitrobenzoic acid. In all three molecules the steric strain is relieved by small out-of-plane displacements of the exocyclic valency bonds in addition to the larger in-plane displacements of these bonds away from one another. Ferguson *et al.* (1962) have also shown that in 2-chloro-5-nitrobenzoic acid the carboxyl group is twisted further out of the benzene plane than in *o*-chlorobenzoic acid.

§4. Racemisation of diphenyl compounds. Since the optical activity of diphenyl compounds arises from restricted rotation, it might be expected that racemisation of these compounds would not be possible. In practice, it has been found that many optically active diphenyl compounds can be racemised under suitable conditions, *e.g.*, boiling in solution. The general theory of these racemisations is that heating increases the amplitude of the vibrations of the substituent groups in the 2 : 2′ : 6 : 6′-positions, and also the amplitude of vibration of the two benzene rings with respect to each other, thereby permitting the substituent groups to slip by one another. Thus the nuclei pass through a common plane and hence the probability



is that the final product will contain an equimolecular amount of the (+)- and (−)-forms. Westheimer (1946–1950) has assumed, in addition to the above bond-stretchings, that the angles α, β and γ are deformed, and also the benzene rings themselves are deformed during racemisation.

The foregoing theory of racemisation is analogous to Werner's theory for the racemisation of compounds which contain an asymmetric carbon atom. According to Werner (1904), the groups in the compound *Cabde* are set vibrating under the influence of heat, and if the amplitude of vibration becomes large enough, all four groups will become coplanar at some instant (Fig. 1). This planar structure is symmetrical, and when the molecule emerges from this condition, there is an equal chance of its doing so

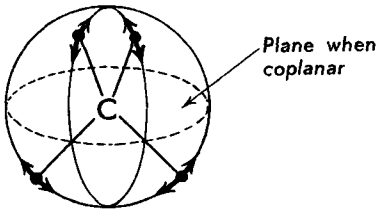
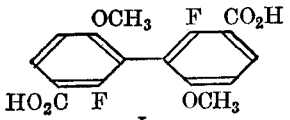


FIG. 5.1.

in the (+)- or (−)-configuration, *i.e.*, the molecule racemises. There is, however, a great deal of evidence against this mechanism in compounds of the type *Cabde*, *e.g.*, from spectroscopic data it appears that the bonds would break before the vibrations were large enough to permit a planar configuration to be reached. Furthermore, Kincaid and Henriques (1940), on the basis of calculations of the energy required for the inversion of molecules, were led to suggest that the molecule *Cabde* can only be racemised by the bonds actually breaking. Even so, this theory of racemisation appears to be the most reasonable one for the racemisation of diphenyl compounds. In this case, the amplitude of vibration does not have to be large in order to permit the *ortho*-groups to slip by one another. This is supported by the fact that it has been found that diphenyl compounds with small substituent groups racemise easily, whereas when the groups are large, racemisation is difficult or even impossible.

2 : 2′ : 6 : 6′-Tetrasubstituted diphenyl compounds may be classified under three headings according to the nature of the substituent groups.

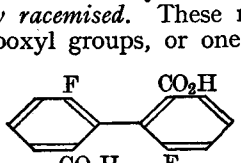
(i) *Non-resolvable.* These contain any of the following groups: hydrogen, methoxyl or fluorine. The volumes (*effective* volumes) of these groups are



I

too small to prevent rotation about the single bond. Thus 2 : 2′-difluoro-6 : 6′-dimethoxydiphenyl-3 : 3′-dicarboxylic acid, I, is non-resolvable.

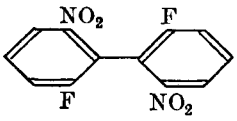
(ii) *Resolvable, but easily racemised.* These must contain at least two amino-groups, or two carboxyl groups, or one amino- and one carboxyl



II

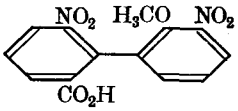
group; the remaining groups may be any of those given in (i) [but not hydrogen]. Thus 6 : 6′-difluorodiphenic acid, II, is resolvable, and is readily racemised.

(iii) *Not racemisable at all.* Diphenyl compounds which fall in this group are those which contain at least two nitro-groups; the other groups can be any of those given in (i)—but not hydrogen—and (ii). Thus 2 : 2′-difluoro-6 : 6′-dinitrodiphenyl, III, is resolvable, and cannot be racemised.

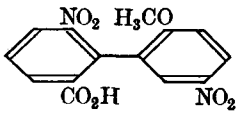


III

In addition to the size of the groups in the *ortho*-positions, the nature and position of other substituent groups also play a part in the rate of racemisation, *e.g.*, the rate of racemisation of IV is much slower than that of V (Adams *et al.*, 1932, 1934). Thus the nitro-group in position 3′ has a much

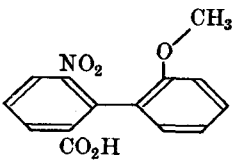


IV

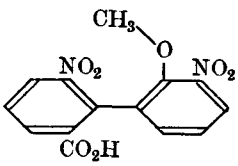


V

greater stabilising influence than in position 5′. The reason for this is uncertain, but one possible explanation is as follows. In VI, the methyl group of the methoxyl group is probably in the configuration shown. In VII, the nitro-group in the 3′-position would tend to force the methyl group away, the resulting configuration being somewhat as shown in VII;



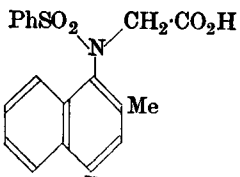
VI



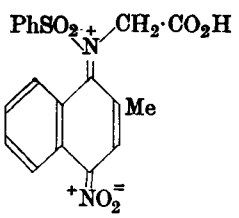
VII

in this condition there would be greater interference between the methoxyl group and the two groups in the other benzene ring.

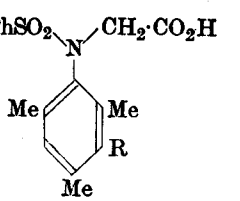
Adams *et al.* (1954, 1957) have examined the rate of racemisation of (VIII). The rate is increased when R is an electron-attracting group such



VIII



IX



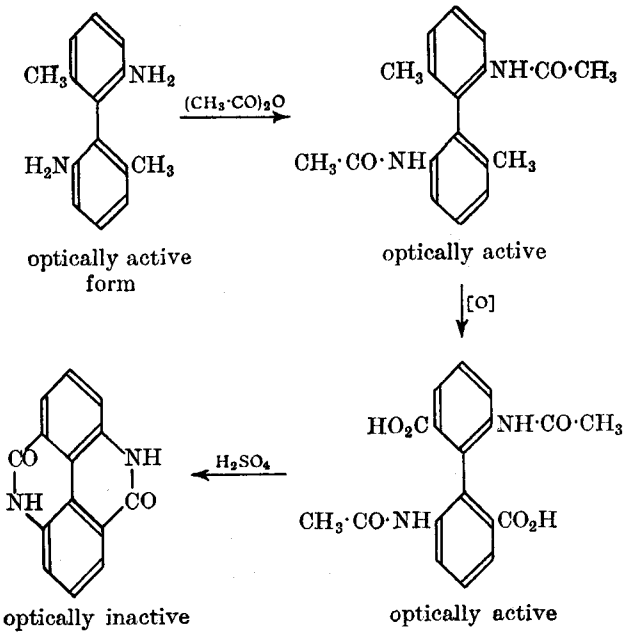
X

as NO_2 or CN, and is decreased when R is an electron-releasing group such as Me or OMe. These results were explained as follows. With, *e.g.*, R = NO_2, (IX) contributes to the resonance hybrid as well as (VIII). The resonance hybrid therefore has increased C=N double bond character

and consequently it is now easier for the molecule to pass through a planar transition state. With, *e.g.*, R = Me, the C—N bond acquires far less double bond character than in its absence, and so it is more difficult for the molecule to pass through a planar transition state.

Adams *et al.* (1957, 1961) also examined the optical stability of compounds of type X; they found that the half-life was in the following order for R: Me < Et < *i*-Pr > *t*-Bu. If the effect of R were due merely to the inductive effect, then the unexpected value for *t*-Bu cannot be explained on this basis. The authors have proposed the following explanation. The *t*-Bu group, because of its large bulk, displaces the adjacent Me groups out of the plane of the benzene ring, thereby causing molecular overcrowding; this decreases the interference to rotation about the N—C (ring) bond (§3a). A molecular model of this compound showed such an interference. According to Bryan *et al.* (1960), it is possible that steric repulsion also operates to cause considerable angle distortion.

§5. Evidence for the obstacle theory. Evidence for the obstacle theory, *i.e.*, interference of groups, amounts to proving that the two benzene rings in optically active diphenyl compounds are not coplanar. A direct chemical proof for the non-coplanar configuration was given by Meisenheimer *et al.* (1927). The method was to unite the " obstacle groups " in optically active diphenyl compounds, thereby forming five- or six-membered rings. Now such systems are known to be planar, and hence optical activity should disappear; this was found to be so in practice. Meisenheimer started with 2 : 2′-diamino-6 : 6′-dimethyldiphenyl, resolved it and then carried out the following reactions on one of the enantiomorphs:



optically active form — optically active — optically active — optically inactive

In all the optically active compounds, the rings *cannot* be coplanar, since if they were, the molecules would possess a centre or plane of symmetry. If the dilactam, however, is *not* planar, then it would possess no elements of symmetry, and consequently would be optically active. If the dilactam is planar, then it has a centre of symmetry, and consequently cannot be

optically active. This compound was, in fact, not optically active, and so must be planar.

According to Dhar (1932), X-ray analysis studies have shown that in the solid state the diphenyl molecule is planar. On the other hand, according to Robertson (1961), who also examined crystalline diphenyl by X-ray analysis, the molecule is *not* strictly planar. This non-planarity has been attributed to steric repulsion between the *o*-hydrogen atoms. Gas phase electron-diffraction studies indicate that the two rings are inclined at about 45° to one another (Brockway *et al.*, 1944; Bastiansen, 1949). In the solid state, crystal forces presumably tend to keep the diphenyl molecule almost planar.

§6. STEREOCHEMISTRY OF THE ALLENES

Allenes are compounds which have the general structure I.

*ab*C=C=C*de* I *ab*C=C=C*ab* II

Examination of the space formula of compounds of this type shows that the molecule and its mirror image are not superimposable. The modern way of writing I is shown in Fig. 2. The two end carbon atoms are in a state of trigonal hybridisation, and the centre carbon atom is in the digonal state. Thus the centre carbon atom forms two π-bonds which are perpendicular to each other; in Fig. 2 the π_x-bond is perpendicular to the

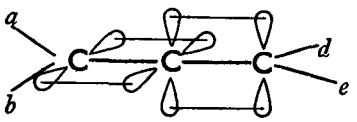
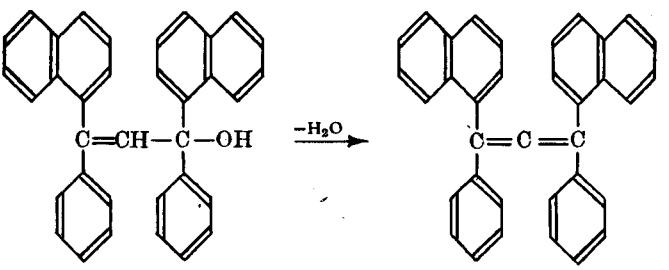


FIG. 5.2.

plane of the paper, and the π_y-bond is in the plane of the paper. In the trigonal state, the π-bond is perpendicular to the plane containing the three σ-bonds (see Vol. I, Ch. II); consequently the groups *a* and *b* lie in the plane of the paper, and the groups *d* and *e* in the plane perpendicular to the plane of the paper. This molecule does not possess a plane or centre of symmetry; this is also true for molecule II. Thus I and II will be resolvable (see also §3. IV).

The resolvability of allenes was predicted by van't Hoff in 1875, but experimental verification was not obtained until 1935, when Mills and Maitland carried out a catalytic asymmetric dehydration on $\alpha:\gamma$-di-1-naphthyl-$\alpha:\gamma$-diphenylallyl alcohol, III, to give the dinaphthyldiphenyl-

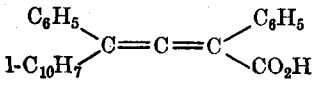


III IV

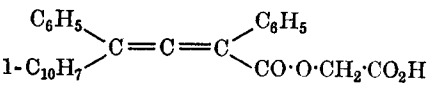
allene, IV. When the dehydration was carried out with an optically inactive dehydrating catalyst, *e.g.*, *p*-toluenesulphonic acid, the racemic modification of the allene derivative was obtained. When, however, the alcohol

III was boiled with a one per cent. benzene solution of (+)-camphorsulphonic acid, a dextrorotatory allene was obtained. Similarly, (−)-camphorsulphonic acid gave a lævorotatory allene.

The first successful *resolution* of an allene derivative was carried out by Kohler *et al.*, also in 1935. Lapworth and Wechsler (1910) prepared γ-1-



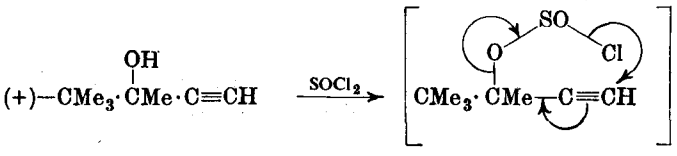
V



VI

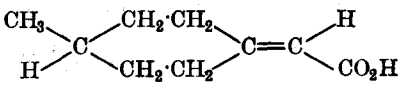
naphthyl-α : γ-diphenylallene-α-carboxylic acid, V, but failed to resolve it; they were unable to crystallise the salts with active bases. Kohler converted this acid into the glycollic acid ester, VI, and was then able to resolve VI by means of brucine.

Landor *et al.* (1959) have prepared an optically active allene by a method which correlates it stereochemically with a tetrahedrally asymmetric alcohol. An optically active acetylenic alcohol, on treatment with thionyl chloride, gave an optically active allene; the mechanism is possibly S_Ni'.



Landor *et al.* (1962) have also deduced the absolute configuration of the (+)-chloride by first determining the absolute configuration of the (+)-alcohol; the (*R*)-(−)-alcohol gave the (*S*)-(−)-allene.

Although allenes were not successfully resolved until 1935, compounds with a *similar* configuration were resolved as early as 1909. In this year,



VII

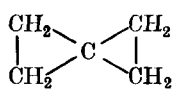
Pope *et al.* resolved 1-methyl*cyclo*hexylidene-4-acetic acid, VII; in this compound one of the double bonds of allene has been replaced by a six-membered ring, and the general shape of the allene molecule is retained.

It is interesting to note, in connection with allenes, that the antibiotic *mycomycin* has been shown to contain the allene grouping. Mycomycin is optically active, and is the only known natural compound which owes its optical activity to the presence of this grouping. Celmer and Solomons (1953) have shown that the structure of mycomycin is:

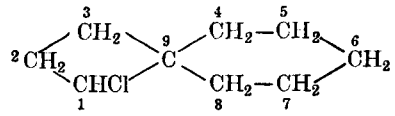
§7. STEREOCHEMISTRY OF THE SPIRANS

If both double bonds in allene are replaced by ring systems, the resulting molecules are *spirans*. One method of naming spirans obtains the root name from the number of carbon atoms in the *nucleus*; this is then prefixed by the term " spiro ", and followed by numbers placed in square brackets

which indicate the number of carbon atoms joined to the "junction" carbon atom. The positions of substituents are indicated by numbers, the



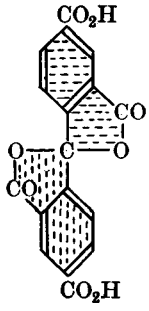
I



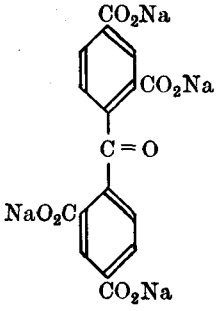
II

numbering beginning with the *smaller* ring and ending on the junction carbon atom; *e.g.*, I is spiro-[2 : 2]-pentane, II is 1-chlorospiro-[5 : 3]-nonane.

Examination of these formulæ shows that the two rings are perpendicular to each other, and hence suitable substitution will produce molecules with no elements of symmetry, thereby giving rise to optically active forms, *e.g.*, Mills and Nodder (1920, 1921) resolved the dilactone of benzophenone-2 : 2′ : 4 : 4′-tetracarboxylic acid, III. In this molecule the two shaded



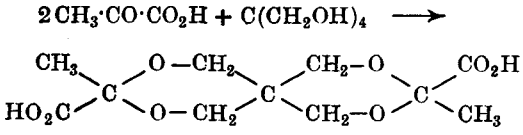
III



IV

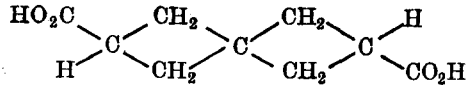
portions are perpendicular to each other, and consequently there are no elements of symmetry. When this compound is treated with sodium hydroxide, the lactone rings are opened to form IV, and the optical rotation disappears.

Böeseken *et al.* (1928) condensed penta-erythritol with pyruvic acid and obtained the spiro-compound V, which they resolved. Some other spiro-

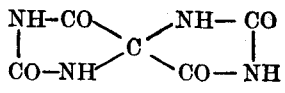


V

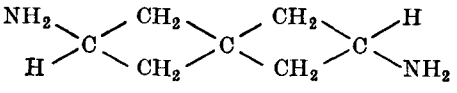
compounds that have been resolved are the spiro-heptane, VI (Backer *et al.*, 1928, 1929), the spiro-hydantoin, VII (Pope and Whitworth, 1931), and the spiroheptane, VIII (Jansen and Pope, 1932).



VI

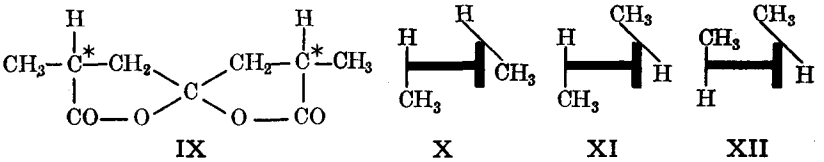


VII



VIII

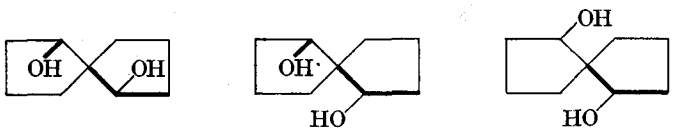
In all the cases so far discussed, the optical activity of the spiran is due to the asymmetry of the molecule as a whole; thus there is only one pair of enantiomorphs. If a spiro-compound also contains asymmetric carbon atoms, then the number of optically active forms is increased (above two), the actual number depending on the compound in question, *e.g.*, Sutter and Wijkman (1935) prepared the spiro-compound IX, which contains two similar asymmetric carbon atoms (*). If we imagine the left-hand ring of IX to be horizontal, then the right-hand ring will be vertical; and if we represent them by bold horizontal and vertical lines, respectively, then



IX X XI XII

there are three different geometrical isomers possible, X, XI and XII (this can be readily demonstrated by means of models). Each of these geometrical isomers has no elements of symmetry, and so each can exist as a pair of enantiomorphs. Three racemic modifications were actually isolated by Sutter and Wijkman, but were not resolved.

Cram *et al.* (1954) have also prepared the following three spiro [4 : 4] nonanediols (as racemates):



cis-cis *cis-trans* *trans-trans*

Various spiro-compounds have been prepared in which the spiro-atom is nitrogen (§2a. VI), phosphorus (§3b. VI), or arsenic (§4a. VI).

A spiran compound, acorone, has now been found in nature (§28c. VIII).

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